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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Article by

LOUIS J. SOFFER,
AARON GUTMAN,
JACK GELLER
and J. LESTER GABRILOVE

MANAGEMENT OF DISSEMINATED NEOPLASTIC DISEASE

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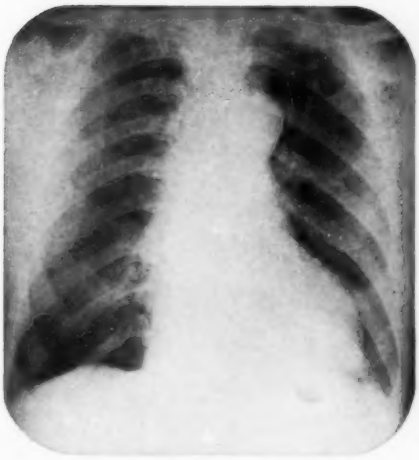

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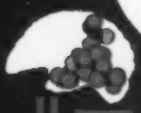

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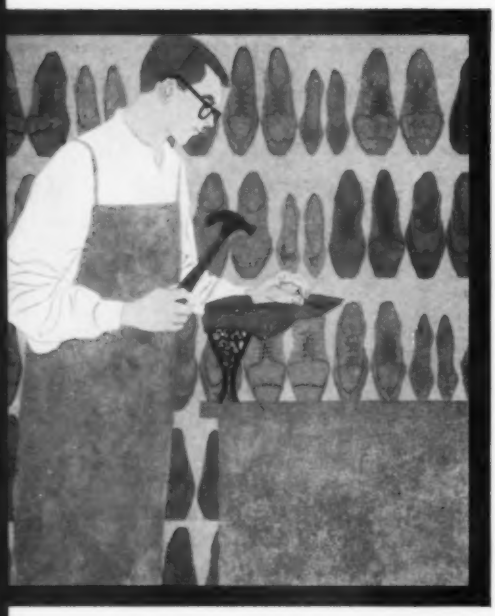

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*Freeman, J. T.: Features of Gerontology's Clinical Future, *J.A.M.A.* 161:948, 1956.

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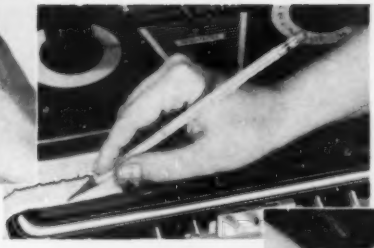

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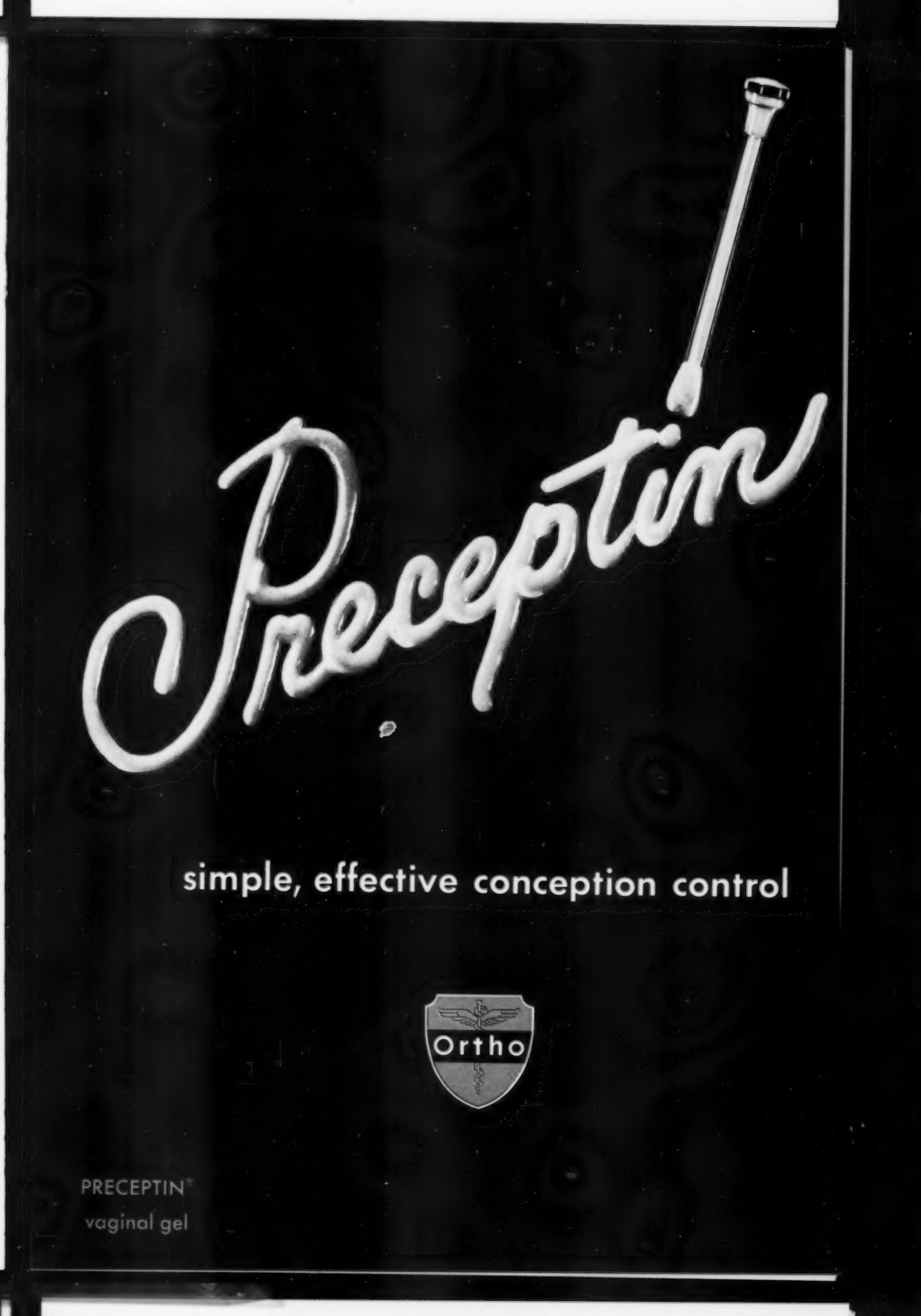
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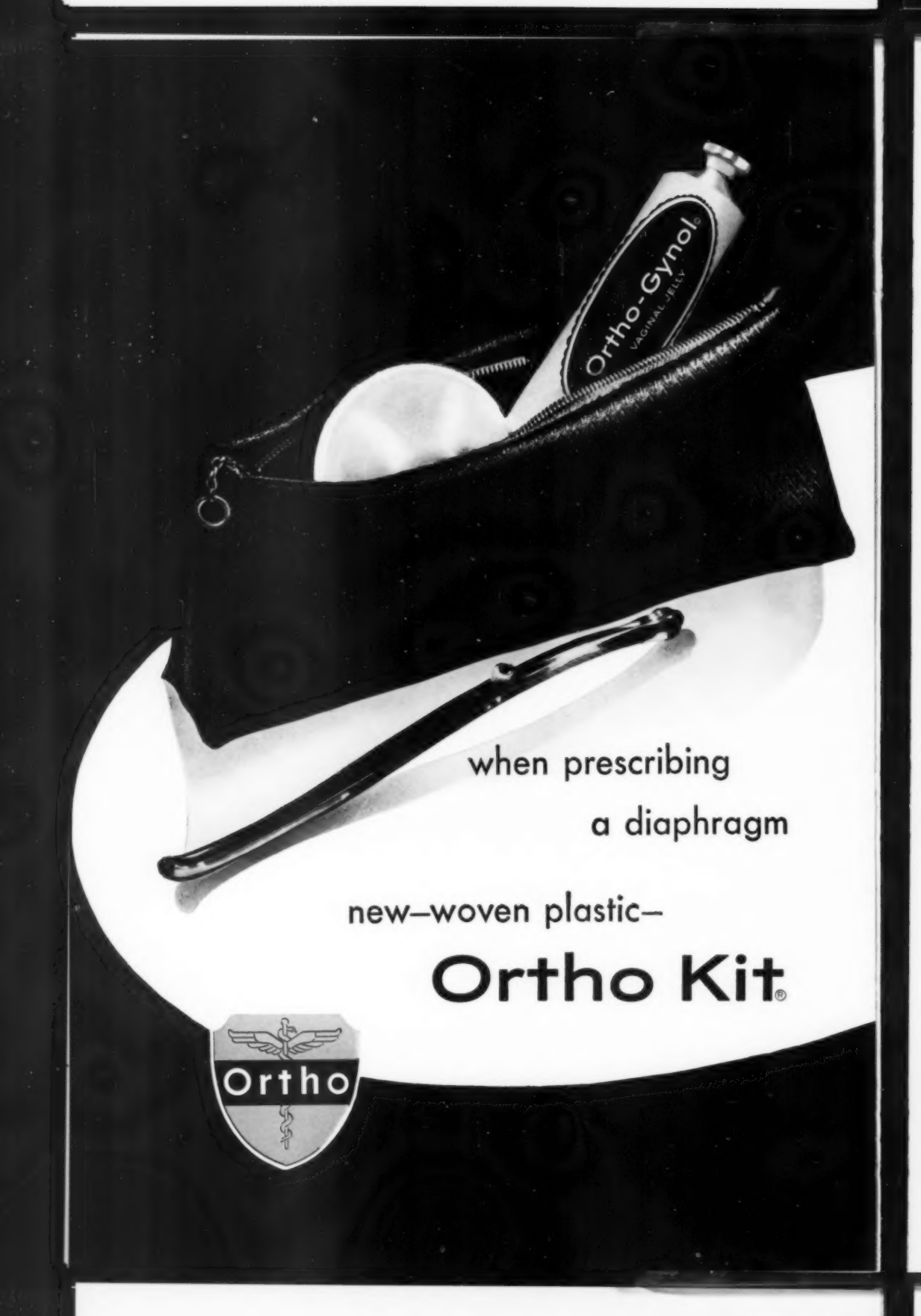
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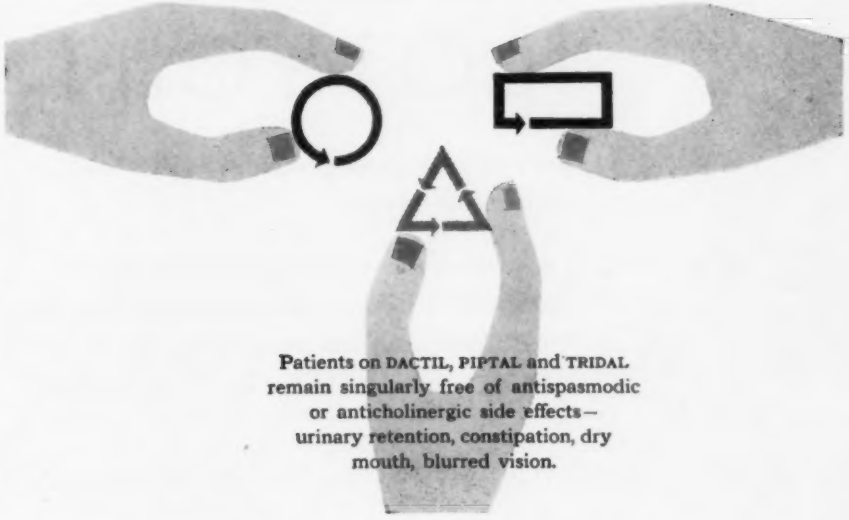

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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OF MEDICINE

VOL. 33, NO. 10 OCTOBER 1957

A COMMUNICATION TO THE FELLOWS OF THE NEW YORK ACADEMY OF MEDICINE

THE Council of The New York Academy of Medicine has directed the President to appoint a committee to survey, in searching fashion, the objectives, functions and activities of the Academy as they exist today. The Survey Committee is also charged with the task of making recommendations concerning future procedure and policies, as well as effective and practical means for executing them.

Such a formal survey has never before been attempted. Some of the more cogent reasons for undertaking it at this time are: first, the organizational and corporate growth of the Academy since its founding one hundred and ten years ago; second, the expansion of its activities, both in medical and adjacent fields; third, a desire to retain the position of leadership which it has attained, not only in the local community, but throughout the nation and abroad. In each of these reasons are implied certain responsibilities which must be met, thoughtfully and with foresight. But an even stronger motive for self-examination is afforded by the altered scene in which the Academy operates. Numerous factors have served to bring about new viewpoints, both lay and professional, toward medicine in the modern world. Among these may be mentioned the impact of insurance, of medical care in industry, of labor union participation, of the educational experiments and pro-

grams in universities and hospitals, the increase in the number of societies devoted to medical specialties, the rise of voluntary health agencies and the growing part played by governmental public health services. There is a general awareness of the importance of basic research. The interplay of professional and lay journalism, as well as the wide potential influence of radio and television, cannot be ignored. The Academy, in order to meet its obligations and render the greatest possible service, must adapt itself to a changing environment.

In compliance with the directive of the Council, your President has appointed the following Fellows as a Survey Committee, under the general chairmanship of Dr. William Barclay Parsons, and each will act as chairman of a subcommittee to study one phase of the activities of the Academy:

Administration:	Marcus D. Kogel
Building & Plant:	Condict W. Cutler, Jr.
Bulletin:	Louis J. Soffer
Finance:	Henry N. Pratt
Library:	George Rosen
Medical Education:	Dickinson W. Richards, Jr.
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This group and its Chairman, Dr. Parsons, constitute an Executive Committee. Comments, critical or otherwise, are earnestly solicited from the Fellows concerning any aspect of the activities or operation of the Academy. Such communications should be addressed to Dr. Parsons or to one of the subcommittee Chairmen to whose particular field of study the comments may appropriately apply; these may be sent to the Academy address.

The Survey Committee will submit its findings and recommendations to the Council for approval and action. It is anticipated that the final report will be ready for publication during the coming year.

It is the sincere hope of the Officers and Council that the entire Fellowship will contribute of its experience and thinking to this project, so that the usefulness of the Academy, to its Fellows, to the medical profession at large and to the community, may be increased.

Robert L. Levy	William Barclay Parsons	Howard Reid Craig
President	*Chairman, Survey Committee*	*Director*

THE ROLE OF ADRENAL STEROIDS ON RENAL FUNCTION AND ELECTROLYTE METABOLISM*

The Fourth Harlow Brooks Lecture

LOUIS J. SOFFER

Attending Physician and Head of Endocrinology, The Mount Sinai Hospital; Clinical Professor of Medicine, State University of New York College of Medicine at New York City

and

AARON GUTMAN,** JACK GELLER*** and J. LESTER GABRILOVE†

THE adrenal cortex is intimately concerned with electrolyte and water metabolism and, either directly or indirectly, with certain aspects of renal function. With the isolation and identification of various adrenal cortical fractions, it became possible to subject this aspect of adrenal function to more precise study. The results of these studies over the past quarter of a century have yielded a voluminous and, by and large, contradictory and confusing literature. Certain generalities have of course become evident. Even prior to the availability of specific adrenal steroidal fractions it had been adequately established that the lack of adrenal function in the patient with Addison's disease and in the adrenalectomized animal resulted in an increased urinary excretion of sodium and chloride with equivalent amounts of water, and a decrease in the urinary excretion of potassium. When this basic defect was later subjected to more careful scrutiny with improved techniques, it became evident that the defect in relation to electrolyte and water metabolism consisted of at least three component abnormalities: 1) a decrease in the glomerular filtration rate and renal plasma flow;[1,2] 2) an inability adequately to handle a water load over a given period of time; and 3) an increase in the urinary loss

*Presented by Dr. Soffer at the 29th Graduate Fortnight of The New York Academy of Medicine, October 23, 1956. On this occasion, Dr. Soffer received the Harlow Brooks Medal.
From the Endocrine Research Laboratory and Clinic of the Department of Medicine and the Department of Chemistry, The Mount Sinai Hospital, New York City.
Aided by a grant from the National Institutes of Health of the U. S. Public Health Service. Research grant number A-921 (R).
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of sodium and chloride and a decrease in the urinary excretion of potassium. The question promptly arose as to whether the inability of the untreated patient with Addison's disease or the adrenalectomized animal to handle a water load represented a renal tubular defect, a reduction in the glomerular filtration rate, a change in the renal plasma flow, or various combinations of these several factors. Similarly, attempts were made to relate the abnormalities in electrolyte metabolism to changes in renal function. When the various adrenal hormones became available, studies were instituted to investigate their individual effects on these specific functions.

The contradictory results of these studies on electrolyte metabolism and renal function are due to a variety of factors, including: 1) the presence or absence of the adrenals; 2) the dosage and duration of treatment; 3) the daily salt intake; 4) the mode of administration; and 5) species differences.

Effects of Adrenal Steroids on Electrolyte Metabolism and Renal Function in Adrenal Insufficiency

In the patient with Addison's disease and in the adrenalectomized animal the administration of desoxycorticosterone is followed by a decrease in the urinary excretion of sodium, an increase in the urinary excretion of potassium, an elevation in the serum sodium level, and a reduction in the serum potassium content. However, despite the ability of this steroid to correct the electrolyte imbalance with respect to sodium and potassium, it fails to exercise an effect on the inability of the adrenalectomized animal or patient with Addison's disease to adequately handle a water load within a given period of time. In addition, the reduction in the glomerular filtration rate and the renal plasma flow cannot be completely corrected by the administration of desoxycorticosterone alone, both during short term studies[3-5] and more prolonged periods of administration.[3] This situation is altered, however, when the degree of hydration is increased appreciably.[3] The reduction in the glomerular filtration rate following upon adrenalectomy can be corrected by adequate maintenance with saline[6] (Table I). Similarly, the administration of excessive amounts of desoxycorticosterone in association with an adequate salt intake may result in an increase in the glomerular filtration rate approximating normal levels providing significant sodium and water retention occurs.[3]

TABLE I—GLOMERULAR FILTRATION RATES OF FIVE DOGS IMMEDIATELY BEFORE AND 8 TO 10 DAYS AFTER ADRENALECTOMY, ADEQUATELY MAINTAINED WITH SALINE

	Glomerular Filtration Rate (ml./min.)	
Dog. No.	*Control*	*After Adrenalectomy*
1	61.8	61.9
2	34.6	31.2
3	53.9	48.7
4	63.3	59.7
5	57.6	61.0

Adapted from Roemmelt, J. C., Sartorius, O. W., and Pitts, R. F.: Excretion and Reabsorption of Sodium and Water in the Adrenalectomized Dog. Amer. J. Physiol., 159:124, 1949. (Ref. 6.)

This is in considerable contrast to the results observed with cortisone. The administration of this agent to adrenalectomized animals results, within a matter of hours, in a significant increase in both the renal plasma flow and glomerular filtration rate. The increase in the glomerular filtration rate thus observed may occur in the absence of any increase in the plasma volume and in the face of a negative sodium balance.[3, 5]

The fact that in adrenal insufficiency the glomerular filtration rate may be enhanced by the adequate administration of saline would suggest that the reduction in glomerular filtration is at least in part related to the loss of sodium and extracellular fluid. Although this is indeed an important factor, the fact remains that cortisone is capable of improving the defect in glomerular filtration over a period of time during which no significant changes in the extracellular compartment or plasma volume could be expected to take place. It is in this sense that its effect on this particular renal function is different from that exerted by desoxycorticosterone. The role of this latter hormone on the glomerular filtration rate is essentially an indirect one, related to its ability to cause a retention of electrolyte and water.

This specificity of effect of cortisone is similarly demonstrated in its influence on the renal response to water loading in adrenal insufficiency. No amount of desoxycorticosterone will increase the five-hour urine volume following the imbibing of a water load. However, under similar

TABLE II—EFFECT OF CORTISONE ON WATER LOADING RESPONSE AND GLOMERULAR FILTRATION RATE IN ADRENAL INSUFFICIENCY

	1500 ml. of water		*1500 ml. of water +50 mg. cortisone*	
Subject	*5 hour urine volume ml.*	*Creatinine clearance (cc./min.)*	*5 hour urine volume (ml.)*	*Creatinine clearance (cc./min.)*
U.D. (A)	390	99	760	97
G.M. (H)	420	89	1025	103
C.S. (H)	217	56	1000	63
S.G. (H)	640	85	980	89

(A) = Addison's disease
(H) = Hypopituitarism with adrenal insufficiency

test circumstances the prior administration of cortisone will invariably result in a significant increase in the urine volume approximating that obtained in normal individuals.[7] This effect of cortisone on the renal response to water loading can apparently occur independently of its effect on the glomerular filtration rate. In Table II are presented the data obtained in one patient with Addison's disease and three patients with hypopituitarism with adrenal insufficiency. In all four patients an appreciable increase in the urine volume occurred following the oral administration of 50 mg. of cortisone two hours before the test. In only one instance, however, was there a concomitant significant increase in the creatinine clearance. This, of course, does not exclude the probable effect of the rate of glomerular filtration on the maximal urinary flow in intact animals.[8] But in adrenal insufficiency there still is an additional factor, that of the influence of some adrenal hormones on the resorptive capacity of the distal tubular segment for water.

The available data would suggest that in adrenal insufficiency, desoxycorticosterone acetate exercises a considerable and fairly consistent effect on electrolyte and water exchange, in part by increasing the tubular reabsorption of sodium. The effects of cortisone on electrolyte metabolism are less consistent but this steroid specifically affects glomerular filtration and alters the resorptive capacity of the distal segment of the tubules for water.

The reduction in the glomerular filtration rate and renal plasma flow in adrenal insufficiency probably represents a homeostatic device to minimize salt and water loss, since one of the major renal defects in adrenal insufficiency is a decrease in the renal tubular absorption of sodium. Following the administration of various adrenal cortical fractions, the urinary loss of electrolyte becomes appreciably reduced, often, however, without any immediate change in the rate of glomerular filtration or renal plasma flow.[9] Conversely, other adrenal hormones may cause an increase in the glomerular filtration rate accompanied by increasing losses of urinary sodium[3,5] despite the fact that the expected enhancement of tubular absorption of sodium from 98 to over 99 per cent has occurred. This paradox may be resolved if we assume that the urine volume and its sodium content under the influence of adrenal steroid therapy are the mathematical resultant of: 1) the degree of change in the glomerular filtration rate; 2) the degree of change in the renal plasma flow; and 3) the degree of change in the absorptive capacity of the tubule for electrolyte and water.

One may further speculate on possible additional factors involved in the renal tubular resorptive capacity for water. In adrenal insufficiency this function is defective and capable of correction by cortisone but not by desoxycorticosterone. That this defect is probably not entirely related to a decrease in glomerular filtration is evidenced by the fact that an appreciable increase in the glomerular filtration rate by the administration of saline and desoxycorticosterone does not result in any improved response to water loading. On the other hand, there is considerable evidence to suggest that there is an actual increase in the tubular reabsorption of water in adrenal insufficiency.[6,10-13] Corey, Silvette, and Britton[14] have postulated that the adrenal cortical and the posterior pituitary hormones exercise antithetical effects. In effect, the adrenal fractions increase water and decrease sodium excretion, while the posterior pituitary antidiuretic hormone causes the reverse phenomenon. Roemmelt, Sartorius and Pitts[6] suggest that the increased urinary excretion of sodium occurring in adrenal insufficiency is a reflection of the effect of the antidiuretic hormone of the posterior pituitary made possible by the absence of adrenal hormones. Finally, several groups of investigators[15-18] have found evidence of increased amounts of an antidiuretic substance in adrenalectomized animals.

Regardless of whether there actually occurs an increase in circulating

TABLE III—THE EFFECT OF ETHYL ALCOHOL ON THE EXCRETION OF A WATER LOAD IN PATIENTS WITH ADRENAL INSUFFICIENCY

	1500 ml. of water	*1500 ml. of water +60 gm. alcohol*	*1500 ml. of water +50 mg. cortisone*
Subject	*5 hour urine volume ml.*	*5 hour urine volume ml.*	*5 hour urine volume ml.*
L.C. (A)	350	135	1190
U.D. (A)	390	435	760
G.M. (H)	420	375	1025

(A) = Addison's disease
(H) = Hypopituitarism with adrenal insufficiency

antidiuretic hormone, the hypothesis that enhanced tubular reabsorption of water is due to the action of an antidiuretic principle in the absence of adrenal hormones is an attractive one. The question arises as to the origin of this principle, and the first point of consideration, of course, is its possible identity with the antidiuretic hormone of the posterior pituitary. In Table III are presented the data obtained in three patients with adrenal insufficiency on whom water load tests were performed following the oral administration of ethyl alcohol. In none of the three did there occur a significant increase in the urine volume following the ingestion of alcohol, such as one might have expected if the active antidiuretic principle were of posterior pituitary origin. These studies included the administration of the total dose of 60 gm. of alcohol just prior to the administration of the water load, and were subsequently repeated distributing the alcohol equally through a 24 hour period before giving the water. Similar results have previously been reported in one patient with Addison's disease and one with hypopituitarism.[19]

One would hardly accept these data as unequivocal evidence negating the hypothesis. However, since ethyl alcohol has been shown to inhibit the release of antidiuretic hormone from the posterior pituitary gland[20-23] these results do raise two salient questions: 1) Is the circulating antidiuretic principle present in adrenal insufficiency of posterior pituitary origin? and 2) If this factor is of pituitary origin does it play the role in adrenal insufficiency outlined for it by the hypothesis? The

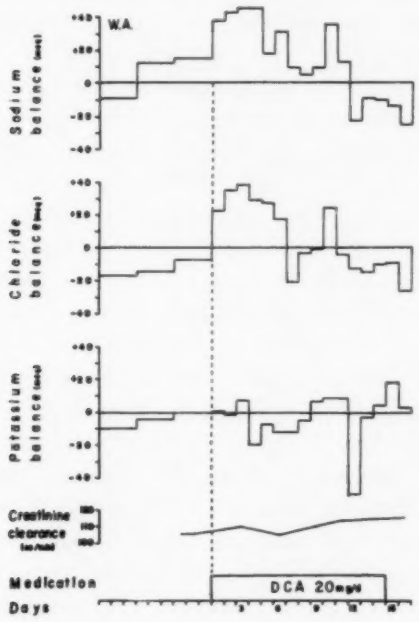

Figure 1—The effect of desoxycorticosterone acetate on sodium, chloride and potassium balance and creatinine clearance in a normal subject.

failure of ethyl alcohol to induce water diuresis following a water load would cast great doubt on the functional significance of the circulating antidiuretic principle in adrenal insufficiency if we assume it to be of posterior pituitary origin.

Effects of Adrenal Steroids on Electrolyte Metabolism and Renal Function in the Presence of Intact and Hyperfunctioning Adrenals

Some years ago we reported on the increased urinary excretion of sodium in some patients with Cushing's syndrome following administration of desoxycorticosterone acetate.[24, 25] This paradoxical observation raised the question of a possible different role of desoxycorticosterone in relation to electrolyte and water metabolism in the presence of intact

adrenals, in contrast to that observed in adrenal insufficiency. Several reports subsequently appeared describing the initial retention of sodium in adrenal intact individuals upon the administration of this hormone, followed by an increased urinary excretion of this electrolyte after 6 to 10 days of continued therapy with the steroid.[26, 27] In one of the reported studies, the salt intake was unrestricted, and in the other, the daily salt intake varied from 3.0 to 3.5 gm. In Figure 1 are presented the balance data that we obtained in a normal subject treated for 14 days with 20 mg. of desoxycorticosterone daily. The subject was maintained on an 8.5 milliequivalent sodium diet with a daily oral supplement of 3 gm. of salt. The period of treatment with desoxycorticosterone was preceded by an eight day control period on the fixed diet with the added daily salt supplement. During the first six days of therapy there occurred a considerable retention of sodium and chloride and some increase in the urinary excretion of potassium. During this six day period the glomerular filtration rate as measured by creatinine clearance remained constant and unchanged from the control period. From the 6th to the 11th day the degree of sodium retention became less. This was more marked with chloride, and a positive potassium balance was observed. From the 11th to the 14th day there was a definite negative sodium and chloride balance and a variable urinary excretion of potassium. From the 6th to the 14th day, concomitant with the increase in the urinary excretion of sodium and chloride, there was a very slight but consistent and progressive increase in the glomerular filtration rate, which reached a peak at the time of the maximum urinary loss of sodium and chloride. Such a progressive decrease in sodium retention with an eventual negative sodium balance within a 6 to 12 day period is not necessarily consistently observed in the presence of intact adrenals. In patients with adrenal cortical hyperfunction producing Cushing's syndrome an increase in the urinary excretion of sodium often, although by no means always, occurs almost immediately upon the administration of desoxycorticosterone.[24, 25] The significance of these observations is to emphasize the difference in effect, at least in time relationships, of the hormone desoxycorticosterone in the presence or absence of intact adrenals. The salt retaining effect of the steroid is in part modified by the presence of actively functioning adrenals.

Unlike desoxycorticosterone, the effect of cortisone on electrolyte metabolism in adrenal insufficiency is variable. In this respect, the be-

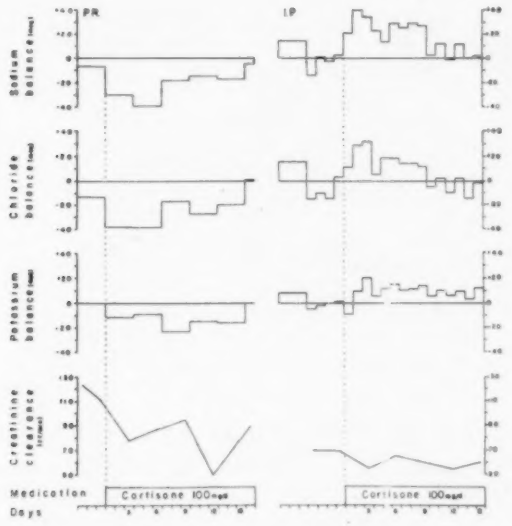

Figure 2—The effect of cortisone on sodium, potassium and chloride balance and creatinine clearance in two normal subjects.

havior of cortisone in the presence of intact adrenals is not very different from that observed in adrenal insufficiency. As with desoxycorticosterone, however, in the presence of intact adrenals the prolonged use of cortisone may result in an increase in the urinary excretion of sodium and chloride, although during the early period of treatment there may have been salt retention.[28, 29] In Figure 2 are presented the balance data that we obtained in two normal subjects treated with the oral administration of 100 mg. of cortisone divided into four equal daily doses, for a 15 day period in one instance and a 17 day period in the other. They were maintained on a constant diet containing 8.5 milliequivalents of sodium with a daily added salt supplement of 3 grams. In the patient P.R. there was an immediate negative sodium, chloride, and potassium balance. The sodium and chloride loss was greatest during the first six days of therapy and then became progressively less, approximating the initial control levels toward the end of the period of study. Throughout the study the glomerular filtration rate, although variable, tended to be lower than during the control period. In the second patient (I.P.) there

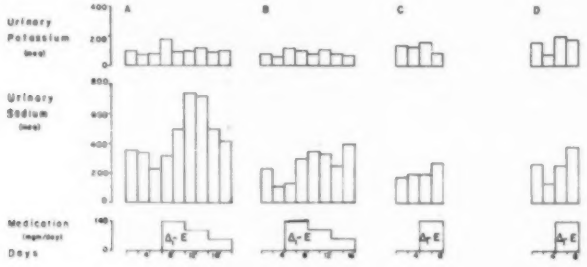

Figure 3—Effect of prednisone on the urinary excretion of sodium and potassium.

was an initial sodium, chloride, and potassium retention, most marked during the first eight days of treatment, followed by a lesser degree of retention of sodium and potassium through the remainder of the study, with a slightly negative chloride balance. The glomerular filtration rate did not alter significantly during the experimental period.

The introduction of an unsaturated double bond between carbons 1 and 2 in ring "A" of cortisone and cortisol alters the effect of the steroid on electrolyte metabolism. In Figure 3 are presented such data in four normal subjects maintained on a constant daily sodium intake of 8.5 milliequivalents with an added supplement of 3.0 gm. of salt. Following a control period of six days on this regimen, they were then given 40 to 140 mg. of prednisone daily by mouth for a 4 to 12 day period. In all four subjects there followed, to varying degrees, an increase in the urinary excretion of sodium and a very slight over-all increase in the urinary excretion of potassium. This study was subsequently repeated in four additional normal subjects, using prednisolone in a daily dosage of 140 mg. for four days (Fig. 4). In three members of this group, there again occurred a definite increase in the urinary excretion of sodium. In the fourth subject, no significant change occurred. In all four subjects the urinary excretion of potassium was slightly increased.

The nature of the changes in the extracellular compartment following administration of cortisone to subjects with intact adrenals is of considerable interest. In such individuals on a comparatively salt-free

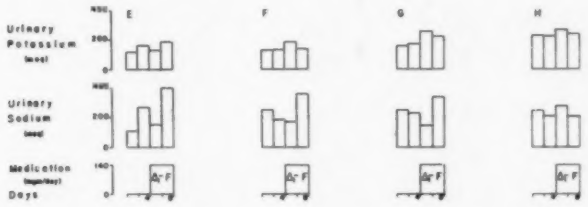

Figure 4—Effect of prednisolone on the urinary excretion of sodium and potassium.

diet (3 to 8.5 milliequivalents of sodium daily) the extracellular compartment was increased following the administration of cortisone. This increase was not associated with a gain in weight, and, therefore, represented a shift of fluid from within the cells outward.[30, 31] Further extension of this study[31] during which subjects with intact adrenals received 100 to 200 mg. of cortisone daily for 10 to 20 days revealed a progressive increase in the inulin space, which reached a peak increase of approximately 23 per cent after eight to nine days and spontaneously reverted to control values by the 12th to 15th day despite continued therapy. The expansion of the inulin space was associated with an increase in total extracellular sodium and chloride but no gain in weight. When the extracellular volume began to fall during the period of treatment there was a proportionate decrease in extracellular electrolytes, not accompanied by a corresponding negative sodium and chloride balance. These data again suggest a transient shift of fluid, sodium, and chloride from within the cell to the extracellular space under the influence of cortisone. Thorn and his co-workers[32] suggest that this effect of cortisone tends to restore towards normal the elevated intracellular sodium characteristic of many chronic disease states. The shift of sodium from within the cell to the extracellular compartment serves to increase the load of sodium presented to the kidney for excretion. Some of the sodium thus presented in the tubule is excreted and the remainder again re-absorbed.

Similar changes in shifts of electrolytes and fluid in the presence of intact adrenals were also obtained with desoxycorticosterone.[33] In one patient with Cushing's syndrome due to adrenal cortical hyperfunction without tumor, however, the oral administration of cortisone was fol-

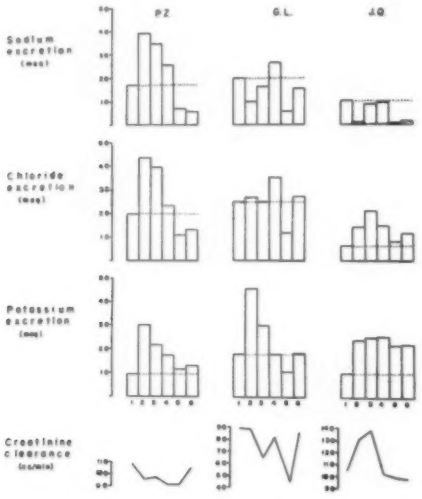

Figure 5—Acute effects of adrenal steroids on urinary excretion of sodium, potassium and chloride: 1) control; 2) cortisone; 3) prednisone; 4) compound "S"; 5) aldosterone; 6) desoxycorticosterone acetate.

lowed by a decrease in the extracellular compartment as measured by thiosulfate; this became evident within three days after the beginning of the experiment and was not associated with a previous increase in the extracellular fluid. In this experiment there occurred no change in the total body water determined by antipyrine, but there was a slight increase in the urinary excretion of sodium and chloride as contrasted to the control balance period. Identical results were subsequently obtained in this patient, employing desoxycorticosterone acetate in place of cortisone.[34] Similar studies conducted in a second patient with Cushing's syndrome yielded results identical in direction with those observed in normal individuals, although the changes were not quite so marked as seen in the latter group.[34]

The variation in effects on electrolyte metabolism in intact subjects under given experimental conditions, observed with the prolonged use of the adrenal steroids, is similarly seen in studies dealing with the acute effects of these fractions. In Fig. 5 are presented the experimental data on the urinary excretion of sodium, chloride, and potassium ob-

tained in three normal individuals following short term administration of cortisone, prednisone, compound "S" (17-hydroxy-11 desoxycorticosterone), aldosterone, and desoxycorticosterone. All patients were maintained throughout the experiment on a constant diet containing 8.5 milliequivalents of sodium with a daily oral supplement of 3 gm. of salt. The subjects were kept on this regimen for four to seven days prior to the beginning of the experimental study. The control values were obtained on the last day of the control period and all steroids with the exception of desoxycorticosterone, were administered two hours prior to the test period. Because of its oily medium, desoxycorticosterone was given four hours before the test. Both aldosterone and desoxycorticosterone were administered parenterally. On the day of the test, breakfast was withheld, and two hours after the administration of the hormone (four hours in the instance of desoxycorticosterone), each subject was given 400 ml. of water to drink; urine collections were then made over a 4-hour period and analyzed for sodium, chloride, potassium, and creatinine. Blood for serum creatinine was withdrawn during the halfmark of the test period. The total test amount of hormone was administered in one dose as follows: cortisone, 150 mg.; prednisone, 50 mg.; compound "S," 150 mg.; aldosterone, 500 micrograms intramuscularly; desoxycorticosterone, 20 mg. intramuscularly. Three days were allowed to elapse after the administration of each fraction before the next hormone was given.

Examination of the data reveals that cortisone and prednisone induced a considerable *increase* in the urinary excretion of sodium in one of the three subjects, and compound "S" in two of the three subjects. Aldosterone and desoxycorticosterone induced a significant *decrease* in the urinary excretion of this electrolyte in all three individuals. The urinary chlorides were increased appreciably in two of the three subjects following the administration of cortisone and prednisone, and in all three with compound "S." A decrease in urinary chloride was noted with aldosterone in two individuals, and in one following the use of desoxycorticosterone. A potassium diuresis was observed to occur in all three subjects when they were given cortisone and prednisone; in two with compound "S"; and in one with aldosterone and desoxycorticosterone. A second subject showed a very slight increase, of questionable significance, in the urinary excretion of potassium following the use of these last two hormones.

The results of the various studies indicate the large variety of factors which determine the nature of the response on electrolyte metabolism to the various adrenal steroids. Some of these factors, such as the presence or absence of the adrenals, the state of hydration, the salt intake, the duration of treatment, and the technical circumstances under which the experiments are performed are quite clear. However, there still remain differences in response when these factors are adequately controlled. In the final analysis, the effect is determined by the sum total of the degree of change in the glomerular filtration rate, the renal plasma flow, and the resorptive capacity of the tubules for water and electrolytes. But the various factors which influence the direction and the degree of the changes in these parameters are by no means clear. More recently, the modification of the chemical structure of the basic adrenal steroid by the organic chemist has served to modify the actions of these fractions. Halogenation of cortisone and cortisol with fluorine or chlorine in the 9 alpha position, or methylation on carbon 2, has increased the sodium retaining effect of the two original hormones enormously, while the introduction of a double bond between carbons 1 and 2 in ring "A" has the reverse effect.

In a general sense, the conclusions are justified that in adrenal insufficiency aldosterone and desoxycorticosterone are salt retaining, while cortisone and cortisol are not consistently so. In those instances in which the latter two hormones do cause a decrease in the urinary excretion of sodium, this effect is not as pronounced as that observed with aldosterone or desoxycorticosterone. Cortisone directly increases the depressed glomerular filtration rate observed in adrenal insufficiency and decreases the resorptive capacity of the renal tubules for water.

In the intact subject both cortisone and desoxycorticosterone will cause an increase in the extracellular fluid compartment, in part due to a shift of fluid and sodium from within the cell outward. The expanded extracellular space will spontaneously contract with the prolonged administration of these agents. In the presence of a spontaneous increase in adrenal cortical function such as occurs in Cushing's syndrome, this homeostatic device, both in regard to the extracellular compartment and the urinary excretion of sodium, is enhanced and may become promptly operative upon exogenous administration of the steroid.

The Meticorten and Meticortelone used in these studies were generously supplied by the Schering Corp., Bloomfield, N. J. Compound "S" by Dr. Elmer Alpert of Merck Sharp & Dohme, Rahway, N. J.; and aldosterone by Ciba, Basle, Switzerland.

REFERENCES

1. Talbott, J. H. Pecora, L. J., Melville, R. S. and Consolazio, W. V. Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary pan-hypofunction, *J. clin. Invest. 21*:107-19, 1942.
2. Waterhouse, C. and Keutmann, E. H. Kidney function in adrenal insufficiency, *J. clin. Invest. 27*:372-79, 1948.
3. Garrod, O., Davis, S. A. and Cahill, G., Jr. The action of cortisone and desoxycorticosterone acetate on glomerular filtration rate, sodium and water exchange in the adrenalectomized dog, *J. clin. Invest. 34*:761-76, 1955.
4. Roberts, K. E. and Pitts, R. F. The influence of cortisone on renal function and electrolyte excretion in the adrenalectomized dog, *Endocrinology 50*:51-60, 1952.
5. Liddle, G. W., Pechet, M. M. and Bartter, F. C. Enhancement of biological activities of corticosteroid by substitution of halogen atoms in 9 alpha position, *Science 120*:496-97, 1954.
6. Roemmelt, J. C., Sartorius, O. W. and Pitts, R. F. Excretion and reabsorption of sodium and water in the adrenalectomized dog, *Amer. J. Physiol. 159*:124-36, 1949.
7. Soffer, L. J. and Gabrilove, J. L. Simplified water-loading test for the diagnosis of Addison's disease, *Metabolism 1*:504-10, 1952.
8. Kleeman, C. R., Epstein, F. H. and White, C. The effect of variations in solute excretion and glomerular filtration on water diuresis, *J. clin. Invest. 35*:749-56, 1956.
9. Pitts, R. F. Effects of adrenal cortical hormones on renal function, *Transactions of Conference on Adrenal Cortex 3*:11-53, 1951. (Josiah Macy, Jr. Foundation.)
10. Gersh, I. and Grollman, A. Kidney function in adrenal cortical insufficiency, *Amer. J. Physiol. 125*:66-74, 1939.
11. Friedman, S. M., MacKenzie, K. R. and Friedman, C. L. Renal function in the adrenalectomized rat, *Endocrinology 43*:123-25, 1948.
12. Lotspeich, W. D. Effect of adrenalectomy on the renal tubular reabsorption of water in the rat, *Endocrinology 44*:314-16, 1949.
13. Gaunt, R., Birnie, J. H. and Eversole, W. J. Adrenal cortex and water metabolism, *Physiol. Rev. 29*:281-310, 1949.
14. Corey, E. L., Silvette, H. and Britton, S. W. Hypophyseal and adrenal influence on renal function in the rat, *Amer. J. Physiol. 125*:444-651, 1939.
15. Martin, S. J., Herrlich, H. C. and Fazekas, J. F. Relation between electrolyte imbalance and excretion of an antidiuretic substance in adrenalectomized cats, *Amer. J. Physiol. 127*:51-57, 1939.
16. Birnie, J. H. and others. An antidiuretic substance in the blood of normal and adrenalectomized rats, *Endocrinology 47*:1-12, 1950.
17. Lloyd, C. W. and Lobotsky, J. Serum antidiuretic substances and urinary corticoidsteroids in the human, *J. clin. Endocrinol. 10*:318-29, 1950.
18. Gaunt, R. Adrenal cortical hormone and related hormones in water metabolism, *Transactions of the Conference on Renal Function*, 1950. (Josiah Macy, Jr. Foundation.)
19. Lamdin, E., Kleeman, C. R., Rubini, M. and Epstein, F. H. Studies on alcohol diuresis. III. The response to ethyl alcohol in certain disease states characterized by impaired water tolerance, *J. clin. Invest. 35*:386-93, 1956.
20. Eggleton, M. G. The diuretic action of alcohol in man, *J. Physiol. 101*:172-31, 1942.
21. Strauss, M. B. Rosenbaum, J. D. and Nelson, W. P. III. The effect of alcohol on the renal excretion of water and electrolytes, *J. clin. Invest. 29*:1053-58, 1950.
22. van Dyke, H. B. and Ames, R. G. Alcohol diuresis, *Acta endocrinol. 7*:110-21, 1951.
23. Kleeman, C. R., Rubini, M. E., Lamdin, E. and Epstein, F. H. Studies on alcohol diuresis. II. The evaluation of ethyl alcohol as an inhibitor of the neurohypophysis, *J. clin. Invest. 34*:448-55, 1955.

24. Soffer, L. J. and others. Utilization of intravenously injected salt in normals and in patients with Cushing's syndrome before and after administration of desoxycorticosterone acetate, *J. clin. Invest. 23*:51-54, 1944.
25. Soffer, L. J., Gabrilove, J. L. and Jacobs, M. D. Further studies on salt tolerance test in normal individuals and in patients with adrenocortical hyperfunction, *J. clin. Invest. 28*:1091-93, 1949.
26. Zierler, K. L. and Lilienthal, J. L., Jr. Sodium loss in man induced by desoxycorticosterone acetate, *Amer. J. Med. 4*:186-92, 1948.
27. Luft, R. and Sjögren, B. Metabolic studies with desoxycorticosterone acetate, *Acta endocrinol. 10*:49-65, 1952.
28. Sprague, R. G. and others. Observations on the physiologic effects of cortisone and ACTH in man, *Arch. intern. Med. 85*:199-258, 1950.
29. Sjögren, B. Changes in total body sodium during prolonged administration of cortisone and desoxycorticosterone acetate, *Acta endocrinol. 10*:40-48, 1952.
30. Soffer, L. J., Levitt, M. F. and Baehr, G. Use of cortisone and adrenocorticotropin in acute disseminated lupus erythematosus, *Arch. intern. Med. 86*:558-73, 1950.
31. Levitt, M. F. and Bader, M. E. Effect of cortisone and ACTH on fluid and electrolyte distribution in man, *Amer. J. Med. 11*:715-23, 1951.
32. Thorn, G. W., Laidlaw, J. C. and Goldfein, A. Studies on the sodium-retaining effect of adrenal cortical steroids, in *The human adrenal cortex*, Boston, Little Brown & Co., 1955, pp. 343-350. (Ciba Foundation Colloquia on Endocrinology, vol. 8.)
33. Guadino, M. and Levitt, M. F. Influence of the adrenal cortex on body water distribution and renal function, *J. clin. Invest. 28*:1487-97, 1949.
34. Soffer, L. J., Eisenberg, J., Lannaccone, A. and Gabrilove, J. L. Cushing's syndrome, in *The human adrenal cortex*, Boston, Little Brown & Co., 1955, pp. 487-504. (Ciba Foundation Colloquia on Endocrinology, vol. 8.)

MONTHLY PANEL MEETINGS FOR THE GENERAL PHYSICIAN

Sixth Series — 1957-1958

(Please Note: For the coming academic year these meetings will be held on the SECOND TUESDAY *of the month, November 1957 through April 1958, at 4:30 p.m., in Room 20 at the Academy.)*

TUESDAY
November 12
1957

MANAGEMENT OF PATIENTS WITH ANGINA

Moderator: Charles E. Kossmann

Members: Clarence E. de la Chapelle
Charles K. Friedberg
Samuel A. Thompson

THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street • New York 29, N. Y.

MANAGEMENT OF DISSEMINATED NEOPLASTIC DISEASE

*Panel Meeting**

DAVID A. KARNOFSKY . . . Moderator

Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, Memorial Center for Cancer and Allied Diseases

Presentations by Panel Members

INFECTION IN DISSEMINATED NEOPLASTIC DISEASE**

MARVIN KUSCHNER

Professor of Pathology and Director of Bellevue Hospital Laboratories, New York University-Bellevue Medical Center

and

LEWIS THOMAS

Professor and Chairman, Department of Pathology, New York University-Bellevue Medical Center

HEMATOLOGIC PROBLEMS†

ALLYN B. LEY

Associate Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, Memorial Center

and

ROSE-RUTH ELLISON

Clinical Assistant, Department of Medicine, Memorial Center, and Research Associate, Cornell University Medical College

METABOLIC DISTURBANCES

W. P. LAIRD MYERS

Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, Memorial Center

THE DIRECT EFFECTS OF CANCER

CHESTER H. SOUTHAM

Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, Memorial Center

* Presented at the 29th Graduate Fortnight of The New York Academy of Medicine, October 16, 1956.
** Presented by Dr. Kuschner.
† Presented by Dr. Ley.

Panel On

MANAGEMENT OF DISSEMINATED NEOPLASTIC DISEASE*

DAVID A. KARNOFSKY . . . Moderator

Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, Memorial Center for Cancer and Allied Diseases

INTRODUCTION

THE panel this afternoon is concerned with the Management of Disseminated Neoplastic Disease in Man. A number of symposia with similar titles have been presented in the past. They have consisted of discussions of the role of surgery, of radiotherapy, and of chemotherapy in the management of cancer; and if sufficient time were available, papers were presented on such subjects as the relief of pain, and the psychological aspects of far advanced cancer. Occasionally a clergyman was asked to explain how people reacted to the threat of impending dissolution. There might be a discussion of what to tell the patient. These are all obviously practical and important subjects; they have already been adequately documented elsewhere.

This panel proposes to examine the management of disseminated neoplastic disease on a different plane; that is, to review the variety of disturbances in the patient produced by the presence of various forms of disseminated cancer. There are admittedly only a few measures available which will restrain the growth of neoplastic cells; these methods at best are of restricted and temporary value. Until more satisfactory specific therapy is discovered, the physician must employ all the knowledge and therapeutic techniques available in an attempt to relieve distress and to prolong life. Steady therapeutic progress (the epoch-making empirical discoveries are excepted) stems mostly from an understanding of the physiopathology of disease.

This panel will undertake to discuss the physiologic and morphologic derangements seen in cancer. It is unfortunate that in many

* Presented at the 29th Graduate Fortnight of The New York Academy of Medicine, October 16, 1956.

instances diagnostic accuracy will not lead to effective therapy, but it is hoped that we can illustrate situations where therapeutic procedures can be instituted with benefit to the patient. Drs. Kuschner and Thomas will describe the problem of infection in patients with widespread cancer. This may be due in part to the disease and in part to the consequences of therapeutic procedures. Drs. Ley and Ellison will review the great variety of hematologic disorders including those of primary neoplasms of the blood-forming organs as well as those changes secondary to the presence of disseminated cancer. Dr. Myers will summarize the variety of metabolic disturbances that are related to the growth of certain forms of cancer, and their presence in specific locations of the body. Finally, Dr. Southam will consider the effects produced by intrusion of metastatic disease on certain organs.

There is not sufficient time to present here the indications for various forms of radiotherapy and list the cancer chemotherapeutic agents. These can be obtained from other sources. This symposium will, I hope, emphasize the variety of problems presented by patients with cancer, and the need for careful analysis of their problem as a prelude to therapy. This will assure the application of the most effective available therapy, and also permit a critical and precise assessment of the effects produced by certain forms of treatment. More important, these clinical situations present intellectual challenges to the physician, which in their solution will contribute to our ability to care for our patients. This is the highest function of medicine.

INFECTION IN DISSEMINATED NEOPLASTIC DISEASE*†

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ANY consideration of infection in disseminated neoplastic diseases would seem to require division of these diseases into two categories; first, carcinomatosis and secondly a category that might conveniently be termed malignant disease of the reticuloendothelial system and which would include malignant lymphoma, leukemia, and multiple myeloma. This separation is not based simply on differences in cell type but rather reflects our belief that these two types of malignant disease are characterized by quite different reactions to infection. Indeed these differences are striking enough to suggest that an examination of them might begin to give us some insight into the factors that determine infectibility.

We should like to consider first infection as a complication of advanced carcinoma. If a large number of cases of this type are examined clinically or at necropsy, infection is found to be a common complication. The type of infection seen, however, leads one to believe that local factors predisposing to infection are far more important than any diminution in general resistance to infection. These local factors are dependent upon alterations in structure and function produced by the tumor itself. They are commonly seen and consist of: 1) ulceration and sloughing of exposed surfaces, as for example in tumors of the gastrointestinal tract, ulcerated tumors of the mouth, or massively ulcerating breast carcinoma; 2) obstruction with stasis and infection

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behind it as in the suppurative pneumonia secondary to bronchogenic carcinoma or pyelonephritis secondary to a variety of pelvic tumors causing ureteral obstruction; 3) perforation, particularly of the gastrointestinal tract, with resulting localized or generalized peritonitis and 4) fistula formation with consequent infection as exemplified by the extension of esophageal carcinoma to the trachea or bronchi and the pulmonary infections secondary to tracheo-esophageal fistula formation as well as the infected rectal and vesical fistulae complicating carcinoma of the cervix. These are only a few examples of the common type of local infection seen in advanced carcinoma. There is nothing specific about them for a foreign body occluding a bronchus or a fishbone perforating the intestine is as likely to produce infection as are tumors at these sites. We have little reason to believe then that the common infections associated with advanced carcinoma reflect any interference with humoral or cellular mechanisms of resistance to infection. Indeed the infrequency with which these common local infections become generalized although accompanied by wide-spread extension of the tumor might well lead one to conclude that the mechanisms of resistance are intact.

Any such conclusion would seem to fly in the face of the fairly widely held belief that severely depleted individuals, of whom the cachectic patient with carcinomatosis is perhaps the prime example, are particularly prone to infection. It is our impression that this belief may be based on a failure to properly evaluate the importance of the local factors we have described and on a too facile interpretation of epidemiological or experimental experience. The epidemiological evidence for increased susceptibility to infection in malnourished, depleted individuals in whom morbidity and mortality from infection reach epidemic proportions frequently fails to take into account the simultaneous neglect of sanitation, the population crowding and the generally inadequate living conditions common to famine areas. There is ample experience, too, which indicates that mass starvation does not lead to mass infection in areas where sanitation control is maintained.[1]

The experimental approach to this problem has concerned itself for the most part with antibody production and susceptibility to infection in animals in which inanition and protein depletion have been induced by deficient diets and/or plasmapheresis. Additional studies have been performed on human subjects with protein depletion secondary

to a variety of diseases. Following the demonstration that antibodies were globulins, Cannon and his associates[2] showed that protein depleted rabbits and rats produced less antibody in response to inoculation with typhoid vaccine and sheep erythrocytes. Similarly protein depleted rats and rabbits immunized with a pneumococcal vaccine had a greater susceptibility to intradermal pneumococcal inoculation than did non-depleted controls.[3] Metcoff and associates[4] on the other hand, demonstrated that rats on protein deficient diets resulting in hypoproteinemia were no less resistant to Salmonella infection than were controls and that the deficient animals attain antibody titers equivalent to those of the controls. In studies by Stoerk, Eisen and John[5] and by Axelrod, Carter, McCoy and Geisinger,[6] specific vitamin deficiencies were shown to influence antibody production but in their low protein and inanition control animals there was no impairment of antibody response. These are some of the apparently inconsistent results of animal investigation and their application to humans must be approached with caution. It is noteworthy that much of the experimental work has been done on animals with degrees of depletion and deprivation so extreme as to be rarely matched in clinical experience.

Turning to the investigations in humans, we again encounter certain inconsistencies. Thus Wohl and co-workers[7] measuring the antibody response to typhoid vaccine by flagellar agglutination found that average titers were highest in patients with normal blood protein levels and lowest in patients with hypoproteinemia secondary to a variety of diseases. Utilizing more quantitative measurements of antibody production during the anamnestic response to diphtheria toxoid, Balch[8] studied a group of 25 severely depleted patients at Bellevue Hospital. Eighteen of these 25 were dying of advanced neoplastic disease. These patients produced antitoxin in amounts equivalent to that produced by a well nourished group and there was no relationship between antitoxin levels and serum albumin or serum globulin levels. Bieler and associates[9] had followed a group of hypoproteinemic anemic patients in their clinic and were struck by the fact that they remained remarkably free of infection. Studies of complement titers, opsonic indices, and antisheep hemagglutinin titers in this group revealed these to be normal. In electrophoretic studies of the serum of these patients, all protein fractions were diminished in quantitative proportions and there was only slight decrease in absolute amounts of gamma globulin. It would seem diffi-

cult then at the present time to implicate inadequate immunologic reaction in the pathogenesis of infections in carcinomatosis.

Rarely, metastatic disease in the bone may be so extensive as to result in a marked decrease in circulating leukocytes. In these patients a type of inadequate response to infection is seen which is termed agranulocytic inflammation. It is characterized by relatively unhindered bacterial growth as demonstrated by the presence of bacterial colonies in a fibrinosanguineous exudate with few or no polymorphonuclear leukocytes present. This type of reaction, or more properly failure of reaction, is much more frequent in the second category of neoplastic disease.

Before considering this second category, it might be well to call attention to one other type of infection seen in patients with advanced carcinoma. At necropsy, some 75 per cent of these patients have lobular pneumonia of varying extent. These pneumonias are usually quite acute and almost agonal in type. Again they are not accompanied by any morphological evidences of disseminated infection. They are no more frequent in patients dying with carcinomatosis than in those dying with cerebral hemorrhage or infarction, brain tumors, cirrhosis, uremia, or congestive heart failure. It is our impression that mechanical and functional factors are of prime importance here too, for, with loss of gag and cough reflexes and depression of normal pulmonary clearing mechanisms, a variety of organisms are aspirated and produce infection. If any general loss of resistance occurs in these moribund patients, it must be considered so nonspecific as to constitute part of dying.

We may now turn to the group with malignant lymphoma, leukemia, and multiple myeloma. In this group, it is immediately obvious that the local factors that predispose to infection in the cases of carcinoma are rarely operative. Luminal obstruction and mucosal surface ulceration are seen from time to time but contribute little to the general problem of infection in these diseases. Considering acute leukemia first, we find that massive terminal infection with septicemia is, or at any rate prior to antibiotics was, a common mode of exitus. Farber[10] describes this in children as follows: "Frequently a trivial cold will progress rapidly within a few hours to a generalized bacteremia and this, at times, despite amounts of antimicrobial agents considered sufficient to control infections of similar nature in nonleukemic children." Kibrick[11] in a study in children with acute leukemia in relapse and re-

mission was able to demonstrate that a diminished antibody response to polyvalent influenza vaccine and formalinized pneumococcal vaccine was characteristic. This is a finding of questionable significance in terms of susceptibility to infection if one measures it against the fact that during hematologic remission, patients with leukemia handle infection as well as do non-leukemics. The implication here is that the leukocytic response or lack of response is of greater importance than a reduced capacity to form antibodies. The older literature reviewed by Forkner[12] describes repeated instances in which patients with chronic, myelogenous or lymphatic leukemia failed to respond to typhoid vaccine. Nevertheless, when massive disseminated infection does occur in these patients, it is usually at a time when the number of normal leukocytes is markedly reduced. This reflects itself in the characteristic agranulocytic response to infection which in turn is correlated with the degree of replacement of normal hematopoietic tissue by tumor. This probably represents only one facet of a more complicated breakdown in mechanisms of defense.

In multiple myeloma, recurrent infections are a not infrequent problem. In our experience, leukopenia is rare in this disease and agranulocytosis, then, does not appear to explain the susceptibility to infection that may be present. Since this is a tumor involving the plasma cells currently thought to have much to do with antibody formation, there have been several studies directed at this feature of the disease. Such studies have demonstrated the total absence of normal gamma globulin in some of these patients,[13] absence or marked depression of so-called natural antibody including antibody to blood group substances,[14] and a generally poor response to specific antigen challenge.[15] Thus some patients with multiple myeloma resemble those with agammaglobulinemia and it would seem justifiable to assume that in this type of patient, failure of antibody formation is at least in part responsible for susceptibility to infection.

Because of the doubts long held by many and still held by some as to the neoplastic nature of Hodgkin's disease, this condition has been the subject of extensive bacteriological investigations. These have contributed nothing to an understanding of the etiology of this form of malignant lymphoma but have yielded interesting information on infection associated with Hodgkin's disease. Many of the organisms reportedly found in association with the disease were of little significance but

it seems reasonably certain that tuberculosis, probably brucellosis in endemic areas, and cryptococcosis are unduly frequent in Hodgkin's disease. Thus Jackson and Parker[16] reported tuberculosis in 20 per cent of their cases of Hodgkin's disease, Forbus and associates[17] reported the presence of Brucella in 14 of 24 cases of Hodgkin's disease and Zimmerman and Rappaport[18] reviewing 60 cases of cryptococcosis at the Armed Forces Institute of Pathology found that 18 occurred in patients with malignant disease of the reticuloendothelial system. Fifteen of these 18 were disseminated cases. It is well known that anergy to tuberculin is usually seen in patients with both Hodgkin's disease and tuberculosis and anergy to abortin is seen in patients with both Hodgkin's disease and brucellosis. One must not assume, however, that this signifies that immunologic paralysis is the basis for susceptibility. In the study by Balch[8] cited above in depleted severely ill patients, two of the cases that gave a good antibody response to diphtheria toxoid were patients with the closely related disease, reticulum cell sarcoma. The evidence seems to be that patients with Hodgkin's disease are curiously susceptible to organisms which normally evoke a reticuloendothelial response. In this regard it is of interest that a number of cases of disseminated histoplasmosis have been reported in association with Hodgkin's disease[19] and we have recently had such a case on our own service. It is conceivable that malignant transformation of the cells of the reticuloendothelial system may impair phagocytosis or other more subtle functions of the mononuclear cell.

There has always been a great deal of interest in the role of the reticuloendothelial system in resistance to infection. The exact nature of this role, however, remains somewhat obscure. In a sense, the involvement of the reticuloendothelial system by tumor might be compared to the phenomenon of so-called reticuloendothelial blockade. If an animal is given quantities of colloidal metal or dyes which are phagocytosed and load the cells, it may be shown that for 16 to 24 hours such an animal is exquisitely susceptible to infection with minute numbers of staphylococci, streptococci, or pneumococci. The significance of this observation is still not clear. Apart from loading the reticuloendothelial cells, such treatment may also affect the properties of the polymorphonuclears, result in reduction of complement, and produce changes in levels of fibrinogen. Further, blockade with one agent does not necessarily interfere with phagocytosis of another agent. Ability or lack of

ability to phagocytose may thus not be the whole story. In this regard it is of interest to consider some of the effects of cortisone and irradiation. The effect that these and other therapeutic agents such as the nitrogen mustards and folic acid antagonists have on susceptibility to infection are eminently pertinent to our discussion since they are so frequently used now in the treatment of malignant disease. These have been the subject of extended investigations and thorough reviews. Since we are attempting specifically to pin-point the relationship between malignant disease and infection, we shall consider some of these agents briefly for the reason that some of their effects seem to be mediated through the reticuloendothelial system and thus they contribute to the evidence that derangements of that system as caused by neoplasia might be expected to impair resistance to infection.

Cortisone, irradiation and nitrogen mustard may, by the lymphoid lysis they induce, interfere with antibody formation. We have, however, indicated, that except for isolated instances it is not clear that infection in neoplasia can be shown to be related to deficient antibody formation.

Leukopenia and particularly agranulocytosis when induced by therapeutic agents may be a real basis for susceptibility to infection and we have called attention to the fact that leukopenia caused by neoplastic replacement of hematopoietic tissue does appear to enhance infection. The extremely rapid breakdown of resistance and natural immunity following experimental treatment with cortisone is not explained by leukopenia, impairment of antibody formation, or reduction in complement. Phagocytosis by reticuloendothelial cells does not appear to be impeded but there is some evidence that the capacity to lyse bacilli is lacking.[20] To a certain extent cortisone rather strikingly duplicates the effects of such blockading agents as thorotrast, colloidal iron, trypan blue, and India ink.[21] Here again there is suggestive evidence that specific impairment of the reticuloendothelial system may interfere with normal defense mechanisms. It has also been suggested that cortisone may influence infection by increasing vasomotor tone and reducing capillary permeability and thus impeding the inflammatory response. By reducing the synthesis of the acid mucopolysaccharide of ground substance, cortisone may interfere with localization of infection. The particular pertinence of the cortisone experience to this discussion is that it demonstrates the complexity of resistance and enforces a sense of caution in explaining susceptibility in terms of a few phenomena which happen

to be currently measurable.

In summary, infection in carcinoma appears to be related to local derangements in structure and function of organs. Except in a few unusual circumstances, there is little evidence at present to implicate defects in the general mechanisms of resistance. Infection in neoplastic disease of the reticuloendothelial system does, on the other hand, appear to be related to impairment of resistance. Defects in some mechanisms of defense explain this impairment in part but it is clear that there is more to resistance than is currently understood. It seems reasonable to hope that further study of infection in neoplasia may contribute to the understanding of the nature of resistance to infection in general.

REFERENCES

1. Keys, A. Caloric undernutrition and starvation, with notes on protein deficiency, *J. Amer. med. Assoc. 138*:500-11, 1948.
2. Cannon, P. R., Chase, W. E. and Wissler, R. W. The relationship of the protein-reserves to antibody-production. I. The effects of a low protein diet and of plasmapheresis upon the formation of agglutinins, *J. Immunol. 47*:133-47, 1943.
3. Wissler, R. W. The effects of protein-depletion and subsequent immunization upon the responses of animals to pneumococcal infection, *J. infect. Dis. 80*: 250-77, 1947.
4. Metcoff, J., Darling, D. B., Scanlon, M. H. and Stare, F. J. Nutritional status and infection response. I. Electrophoretic, circulating plasma protein, hematologic, hematopoietic, and immunologic responses to Salmonella typhimurium (Bacillus aertrycke) infection in the protein-deficient rat, *J. Lab. clin. Med. 33*:47-66, 1948.
5. Stoerk, H. C., Eisen, H. N. and John, H. M. Impairment of antibody response in pyridoxine-deficient rats, *J. exp. Med. 85*:365-71, 1947.
6. Axelrod, A. E., Carter, B. B., McCoy, R. H. and Geisinger, R. Circulating antibodies in vitamin-deficiency states: I. Pyridoxin, riboflavin, and pantothenic acid deficiencies, *Proc. Soc. exp. Biol. Med. 66*:137-40, 1947.
7. Wohl, M. G., Reinhold, J. G. and Rose, S. B. Antibody response in patients with hypoproteinemia, *Arch. intern. Med. 83*: 402-15, 1949.
8. Balch, H. H. Relation of nutritional deficiency in man to antibody production, *J. Immunol. 64*:397-410, 1950.
9. Bieler, M. M., Ecker, E. E. and Spies, T. D. Serum proteins in hypoproteinemia due to nutritional deficiency, *J. Lab. clin. Med. 32*:130-38, 1947.
10. Farber, S. The effect of therapy on the life history and biologic behavior of leukemia, *Proc. Inst. Med. Chicago 18*: 311-25, 1950-51.
11. Kibrick, S. Cited by Farber, Personal communication.
12. Forkner, C. E. *Leukemia and allied disorders*. New York, The Macmillan Co., 1938.
13. Porges, R. F. A method for demonstrating secondary agammaglobulinemia in patients with multiple myeloma, using paper electrophoresis, *J. Lab. clin. Med. 47*:960-68, 1956.
14. Lawson, H. A. and others. Observations of antibody content of blood in patients with multiple myeloma, *New Engl. J. Med. 252*:13-18, 1955.
15. Zinneman, H. H. and Hall, W. H. Recurrent pneumonia in multiple myeloma

and some observations on immunologic response, *Ann. intern. Med. 41*:1152-63, 1954.

16. Jackson, H. and Parker, F. *Hodgkin's disease and allied disorders.* New York, Oxford University Press, 1947.
17. Forbus, W. D. and others. Studies on Hodgkin's disease and its relation to infection by Brucella (abstract), *Amer. J. Path. 18*:745-46, 1942.
18. Zimmerman, L. E. and Rappaport, H. The occurrence of cryptococcosis in patients with malignant disease of the reticulo-endothelial system, *Amer. J. clin. Path. 24*:1050-72, 1954.
19. Zimmerman, L. E. Fatal fungus infections complicating other diseases, *Amer. J. clin. Path. 25*:46-65, 1955.
20. Lurie, M. B., Zappasodi, P., Dannenberg, A. M., Jr. and Cardona-Lynch, E. The effect of cortisone and ACTH on the pathogenesis of tuberculosis, *Ann. N.Y. Acad. Sci. 56*:779-92, 1953.
21. Thomas, L. Cortisone and infection, *Ann. N.Y. Acad. Sci. 56*:799-814, 1953.

MANAGEMENT OF DISSEMINATED NEOPLASTIC DISEASE: HEMATOLOGICAL PROBLEMS*

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As does the management of other manifestations of disseminated neoplastic disease, the proper management of the hematological problems requires insight into the mechanism involved in each individual problem. Neoplasms may produce anemia, for example, in a variety of ways, and appropriate treatment in any individual case will depend on which particular mechanism is responsible. Each case should, therefore, be studied as a fresh problem for which a fruitful and gratifying solution may be found. Such an approach will result in the maximum benefit to the patient and in the greatest satisfaction to the physician.

In this paper an attempt will be made to discuss the problems encountered according to the mechanism of their development, in so far as this is known. Therapeutic indications will thus be arrived at on a rational basis.

THE ANEMIAS (Table I)

Iron deficiency anemia is, of course, extremely frequent in patients with cancer, particularly with lesions of the gastrointestinal tract. While transfusions can always repair such a red cell defect, the simple and inexpensive administration of iron salts by mouth may give rapid and significant palliation in spite of a moderate, continuing blood loss.[1, 2] It should be emphasized, however, that the findings usually associated with iron deficiency anemia should be sought. When the hematological picture is still not conclusive, a therapeutic trial should be performed and the result conscientiously evaluated. Although the continued unindicated use of iron salts by mouth is probably without significant hazard, such a regimen frequently adds an unnecessary burden to a

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TABLE I—ANEMIAS IN PATIENTS WITH DISSEMINATED CANCER

Iron Deficiency
Megaloblastic
Myelophthisic
Hemolytic
"Myelopathic"

TABLE II—PERIPHERAL BLOOD IN MYELOPHTHISIC ANEMIA[a]

Nucleated RBC	18/18
Immature WBC	18/18
Thrombopenia	16/18
Reticulocytosis	13/18
Leukocytosis	2/18
Leukopenia	2/18

patient who may already be taking other medications each day and who may already be having difficulty enough with appetite and gastrointestinal tranquillity.

Megaloblastic anemia is rarely associated with advanced cancer; and when the association does occur, it may be considered fortuitous—except in patients who have undergone total or nearly total gastrectomy for gastric cancer, whether or not their cancer has recurred. Several studies in the past three years[3-5] have repeatedly demonstrated a defect in intrinsic factor secretion in patients with total gastrectomy entirely analogous to the defect in classical pernicious anemia. These studies along with others on the effect of vitamin B_{12} therapy in such patients have made it quite clear that the prophylactic postoperative use of parenteral B_{12} therapy is as strongly indicated as in patients with the usual type of pernicious anemia.

While the anemia associated with disseminated cancer cannot usually be ascribed to replacement of the bone marrow by the neoplastic process and its accompanying fibrosis, such replacement does occasionally occur and gives rise to a distinctive hematological picture, which is indistin-

Figure 1

guishable from that observed with bone marrow replacement due to other causes. Such *myelophthisic anemias* may occur rarely with a variety of neoplastic lesions but are seen most commonly in the course of carcinomas of the breast and prostate. Some indication of the frequency may be gained by the fact that during a one year period at Memorial Center, we observed 18 such instances in patients with metastatic mammary carcinomas.[6]

The distinctive characteristics of this type of anemia (Table II) is the presence of immature granulocytes and nucleated red cells in the peripheral blood. Other findings in the peripheral blood are also listed in the table. The presence of the nucleated red blood cells (sometimes more numerous in the peripheral blood than leukocytes), the clinical background of cancer, and the almost invariable radiological evidences of osseous metastases (17 of our 18 cases) should clearly distinguish this type of anemia from others. In addition, in about half the cases cancer cells may be demonstrated in bone marrow aspirates (Fig. 1)

TABLE III—HEMATOLOGICAL RESPONSES TO THERAPY IN MYELOPHTHISIC ANEMIA OF CANCER[a]

No. Cases Responding	7/17
Castration response	2/8
Androgen response	2/6
Cortisone response	2/9
Hypophysectomy response	2/4
Survival of responders	4.8 mo.
Survival of non-responders	1.1 mo.

The two principal clinical hematological problems such patients present are those relating to the anemia, or deficit in red cell mass, and those relating to thrombocytopenia. Fourteen of our 18 patients presented evidence of abnormal bleeding, ranging from minor intracutaneous bleeding to exsanguinating hemorrhage from the gastrointestinal tract. While temporary improvement in the bleeding tendency can sometimes be obtained by some method of platelet transfusion, in general only by affecting the primary disease can any substantial correction be made of the hemorrhagic state.[7]

That such efforts are useful in palliative therapy has repeatedly been demonstrated in the hematological improvement that accompanies the tumor response in patients with prostate and mammary cancer who are treated by some form of hormonal manipulations, either by the administration of appropriate hormone preparations or by surgical ablative procedures (Table III). Not only may the hematocrit levels rise, but platelet counts may also increase and the bleeding tendency cease. It should be pointed out that the operative procedures in our series[6] were frequently performed in the face of thrombocytopenia, even with frank manifestations of defective hemostasis. In only one of the ten operated patients in our study did bleeding occur from the operative site, and this was relatively easily controlled.

While recent studies[8-11] have almost uniformly demonstrated a decrease in erythrocyte survival time in patients with disseminated neoplastic disease of either lymphomatous or carcinomatous origin, *classical* or *overt hemolytic anemia* with acholuric jaundice, marked reticulocytosis, and "auto-sensitization" of the red cell is much less common, and

TABLE IV—HODGKIN'S DISEASE + OVERT HEMOLYTIC ANEMIA
EFFECT OF LOCAL X-RAY THERAPY

Date	*Hematocrit*	*Reticulocytes*	*Coombs Test*
1/18/56	27.0%	8.0%	4+
	X-RAY THERAPY TO SPLEEN 1/21/56-2/12/56		
2/14/56	38.5%	4.4%	4+
6/11/56	53.5%	1.2%	4+

occurs almost solely in the lymphomatous diseases, particularly chronic lymphatic leukemia. In Wasserman's series[10] the incidence of such anemia in chronic lymphatic leukemia amounted to about 15 per cent. It is less common in lymphosarcoma and Hodgkin's disease and quite rare in chronic granulocytic leukemia; there are only about 12 cases reported[12] in which this kind of overt hemolytic anemia has been found in association with disseminated carcinoma. It may occur at any time in the course of these diseases and occasionally is the presenting manifestation. It should be emphasized that frequently the hemolytic process is the most threatening of the patient's problems; and if it can be controlled, the patient's life expectancy and comfort can be very considerably extended.

Until ACTH, cortisone, and like agents were available, the results of treatment of this complication were irregular. It should be emphasized, however, that the treatment of the primary disease process by conventional x-radiation or by appropriate chemotherapeutic agents such as HN2 or TEM will frequently produce substantial decrease in the hemolytic activity and consequent complete remission of the anemia.

This is illustrated in Table IV, which shows the hematocrit and reticulocyte values in a patient with long-standing quiescent Hodgkin's disease who rather suddenly developed anemia and mild jaundice. There was no lymphadenopathy; and his spleen was not palpable but, on radiological examination, did appear enlarged. For reasons that are not pertinent here, it was deemed inadvisable to treat the patient with corticosteroids. Accordingly, he received a course of x-ray therapy to the left upper quadrant. His response is shown in the table. It is noteworthy

that his direct Coombs test was and has remained strongly positive.

Similar remissions have been observed in other patients treated with x-ray to lymph node enlargements not associated with the spleen and in still others treated with nitrogen mustard or TEM.

While such procedures are occasionally useful in managing these hemolytic states, the treatment of choice, as in idiopathic acquired hemolytic anemia, is the administration of corticosteroids. Not only will these agents frequently measurably affect the primary disease, especially chronic lymphatic leukemia, but they appear to have a separate and distinct effect on the hemolysis itself, regardless of the effect on the other manifestations of the neoplastic disease. In Wasserman's series[10] substantial improvement in the hemolytic anemia was obtained in over 60 per cent of the patients as contrasted with the 10-20 per cent of patients treated only by other methods.

In actual practice it would seem most reasonable, when confronted with such a patient, to initiate treatment with ACTH or one of the cortisone derivatives and practically simultaneously to take measures directed against the primary disease. A word of caution against this program should be mentioned, however. In the occasional patient with relatively advanced disease, particularly with chronic lymphocytic leukemia, whose bone marrow appears to show little erythropoietic activity, the use of generalized agents like HN2 may destroy or at least inhibit what red cell production remains. In these instances it would appear hazardous to use a potentially myelodepressive agent like nitrogen mustard or TEM.

There seems little evidence to support the use of ACTH preferentially over cortisone or prednisone. Most patients will respond to either one equally well when allowances are made for dosage factors. The fact that the corticosteroids may be taken by mouth is a substantial advantage under most circumstances.

The role of splenectomy in this situation is of some interest. Occasionally, gratifying results have followed such a procedure,[13, 14] but the availability of other modes of therapy has mitigated the usefulness of splenectomy. On relatively rare occasions, however, when other therapy has not been successful, removal of the spleen may promote a satisfactory remission.

A word should be added about blood transfusions. The most frequent reaction of a physician to a patient with a moderate or severe

anemia is to order transfusions. In hemolytic anemia of this type, however, not only may transfusions be of very limited use but the hazard may be appreciable. Most of those patients will reach a point where their erythropoietic production is equivalent or nearly so to their rate of red cell destruction. At this point their red cell mass will be practically stable. Provided this level is compatible with freedom from symptoms while at rest in bed, it is preferable to withhold transfusion and to wait for the effects of other forms of treatment to become manifest. In the first place, the transfused blood is usually rapidly destroyed so that the net gain in increasing the red cell mass by any given amount may be negligible and transient. In the second place, the dangers of hemolytic transfusion reactions may be increased, due to the presence of demonstrable hemagglutinins. While such alarming reactions have not been observed in our patients, the possibility of their occurrence seems substantially increased. This is not to say that urgent indications for blood transfusion should be disregarded, but to counsel restraint. We have, indeed, sometimes transfused patients with alarming symptoms directly ascribable to the anemia, even in the face of outright incompatibility by *in vitro* tests. We do it, however, with bated breath and we seek other forms of therapy to let us out of the dilemma as rapidly as possible.

When the other types of anemia associated with disseminated neoplastic diseases are excluded, there are still large numbers of patients with cancer who have an otherwise unexplained anemia. In a series of 116 patients with anemia and advanced cancer studied by Shen and Homburger,[2] 56 per cent had no evidence of blood loss, overt hemolysis, or nutritional deficiency. This kind of anemia was termed the *myelopathic anemia* of cancer. While a few in this series might be classified as myelophthisic anemia, it was a point of special interest that there were more instances of this unexplained anemia in patients without evidence of osseous metastases than in patients with such evidence. This would clearly imply that this myelopathic anemia is not usually related to bone marrow replacement.

The possibility has been raised that this type of anemia is primarily hemolytic in type because of the observation of decreased erythrocyte survival times in such patients. This increase in red cell destruction is rarely very marked, however, and is one for which a normal individual can readily compensate by increasing his rate of erythropoiesis. That

the marrows in such patients do have additional reserve was shown in the studies of Shen and Homburger[2] on the effect of the oral administration of cobalt. There was an almost invariable reticulocyte or hematocrit response in the patients who could tolerate the drug, but the elevation of hematocrit persisted only so long as the cobalt was continued; and this hematologic improvement was not associated with any demonstrable effect on the primary disease. It would appear from this study that the bone marrow in these patients was not operating at full capacity and that the fundamental defect was neither excessive hemolysis nor the limitation of the marrow potential. Rather it would appear that the mechanism responsible for setting the level of erythropoiesis was at fault, just as a dwelling may be too cold because the thermostat controlling the furnace is set too low.

Treatment of this kind of anemia depends on treating the primary disease. Any therapy affecting the primary disease—whether chemotherapeutic, radiotherapeutic or hormonal—will probably proportionately affect the anemia. In the absence of specific indications it is useless to administer iron, vitamin B_{12} or any other hematinics. While the administration of cobalt may improve the hematocrit, it rarely, if ever, improves the patient and may be comparable to placing the patient in a low oxygen atmosphere. The use of cortisone is not recommended unless there is reason to believe it may affect the primary tumor, as it occasionally does breast cancer. The use of transfusion is rarely indicated because in most instances the anemia is not severe enough to cause symptoms, and hematocrit levels will be maintained above the symptomatic level without transfusion. The practice of giving transfusions as a "tonic" is, of course, to be condemned.

Leukopenia

While leukopenia occasionally occurs in patients with untreated disseminated neoplastic disease of either carcinomatous or lymphomatous origin, it seldom offers a significant problem in the management of the patient. The problem does arise occasionally in patients with untreated acute leukemia and, less frequently, in Hodgkin's disease, where therapy with myelodepressive agents, such as antimetabolites or alkylating agents, may seem otherwise indicated. The determining factor governing treatment in these instances should be the cellularity of the bone marrow rather than that of the peripheral blood, which latter

may be diminished by increased peripheral leukocyte destruction or by tissue sequestration directly related to the activity of the primary disease. Provided that the bone marrow appears at least normally cellular, there should be no limitation in using the potentially myelodepressive therapy in order to treat the primary process. Indeed, the return of the peripheral white blood cell count towards normal after treatment is sometimes an indication of a beneficial response.[15]

Leukemoid Reactions

The occurrence of inordinate elevations of the peripheral white blood cell count in patients with widespread cancer has been recognized since attention was drawn to the association by Krumbhaar in 1926.[16] Elevations in excess of 50,000 per cubic millimeter and reaching above 100,000 are seen a few times each year at Memorial Center.[17] While they are almost always granulocytic in character, one patient has been observed with a predominantly lymphocytic response, mimicking chronic lymphocytic leukemia, in the presence of gastric carcinoma, as has also been reported from other institutions.[18,19] The only difficulty such reactions offer is that of distinguishing a benign leukocytosis from a leukemic process. In our experience, these inordinate reactions have occurred almost entirely in patients with disseminated and far advanced carcinoma. The relative maturity of the cells in the peripheral blood and relatively orderly maturation of the progenitors in the bone marrow are helpful but by no means certain indications of the nonleukemic nature of these reactions. The presence of "toxic granulations" in the more mature normal granulocytes and, more particularly, the distinctive alterations in alkaline phosphatase content of the leukemic granulocytes[20,21] should be of differential diagnostic value.

Thrombocytopenia

Thrombocytopenia is one of the frequent and serious complications of disseminated neoplastic disease. This complication usually follows displacement of the megakaryocytes from the marrow either by the primary disease, as in myelophthisic anemia and in chronic or acute leukemia, or by extensive radio- or chemotherapeutic efforts.

Treatment of such thrombocytopenias and the consequent bleeding tendencies is, in general, very unsatisfactory. The relatively short survival of even normal platelets, the difficulties in transfusing fresh

viable platelets even with non-wettable transfusion systems, the rapid dilution of the transfused platelets, and the possible presence of platelet isoantibodies in the recipients all make platelet transfusions of dubious practical effectiveness. While such transfusions should, on the basis of experimental studies,[22] be effective in helping to raise the platelet count and to control bleeding at least for periods up to a week or more, the results in our actual clinical experience at Memorial Center are inconstant at best. Recent reports of the use of preserved concentrated platelet material[23] are of considerable interest; but at the moment such material is not readily available and its clinical utility remains unsettled. At present, no form of substitution therapy is of benefit for more than a few days at a time at best; and, hence, such therapy seems logically limited to the relatively unusual patient who may reasonably be expected to resume normal platelet production after a short interval. It should be emphasized that the most effective method of relieving the thrombocytopenia in these situations is by treating the primary disease, either by appropriate hormonal manipulations in the myelophthisic thrombocytopenias associated with disseminated carcinoma, or by appropriate chemotherapy in patients with leukemic or lymphomatous diseases. On occasion, the use of corticosteroids may benefit the bleeding manifestations even without demonstrable effect either on the platelet count or on other manifestations of the disease.

Recently, platelet agglutinins, presumably leading to an "autoimmune" thrombocytopenia, have been reported in patients with widespread cancer.[24,25] It is not clear, however, how frequent this mechanism of increased peripheral platelet destruction is of significance in the thrombocytopenias seen in patients with advanced neoplastic disease. When it can be demonstrated or seems likely to exist, it would seem reasonable, by analogy with secondary "autoimmune" hemolytic anemia, to administer corticosteroids. Splenectomy has been performed in two such instances, one without benefit[24] and once with indeterminate results.[25]

Summary

Patients with disseminated neoplastic disease may present a variety of hematological abnormalities. These secondary manifestations frequently contribute to the patient's symptoms and sometimes are the cause of the patient's chief complaint. Treatment in some instances at

least, may produce gratifying palliation; but appropriate choice of therapy will depend on an understanding of the mechanism by which the particular abnormality has developed.

REFERENCES

1. Heath, C. W. Treatment of anemia in inoperable carcinoma of stomach, *Med. Clin. N. Amer. 19*:1183-90, 1935.
2. Shen, S. C. and Homburger, F. Anemia of cancer patients and its relation to metastases to bone marrow, *J. Lab. clin. Med. 37*:182-98, 1951.
3. Ley, A. B. and Sharpe, L. E. Absorption of vitamin B_{12} after total gastrectomy (abstract), *Clin. Res. Proc. 2*:31, 1954.
4. Halsted, J. A., Gasster, M. and Drenick, E. J. Absorption of radioactive vitamin B_{12} after total gastrectomy, *New Engl. J. Med. 251*:161-68, 1954.
5. Glass, G. B. J., Boyd, L. J. and Gellin, G. A. Surface scintillation measurements in humans of uptake of parenterally administered radioactive vitamin B_{12}, *Blood 10*:95-114, 1955.
6. West, C. D., Ley, A. B. and Pearson, O. H. Myelophthisic anemia in cancer of breast, *Amer. J. Med. 18*:923-31, 1955.
7. Rundles, R. W. and Jonsson, U. Metastases in bone marrow and myelophthisic anemia from carcinoma of prostate, *Amer. J. med. Sci. 218*:241-50, 1949.
8. Ley, A. B., Rivers, S. L. and Mayer, K. Erythrocyte survival in neoplastic disease (abstract), *Proc. Amer. Assoc. Cancer Res. 2*:31, 1955.
9. Hyman, G. A. and Harvey, J. E. Pathogenesis of anemia in patients with carcinoma, *Amer. J. Med. 19*:350-56, 1955.
10. Wasserman, L. R., Stats, D., Schwartz, L. and Fudenberg, H. Symptomatic and hemopathic hemolytic anemia, *Amer. J. Med. 18*:961-89, 1955.
11. Rosenthal, M. C. and others. The autoimmune hemolytic anemia of malignant lymphocytic disease, *Blood 10*:197-227, 1955.
12. Ley, A. B. Mechanisms of anemia in cancer, *Med. Clin. N. Amer. 40*:857-70 (May) 1956.
13. Welch, C. S. and Damesheck, W. Splenectomy in blood dyscrasias, *New Engl. J. Med. 242*:601-06, 1950.
14. Sykes, M. P., Karnofsky, D. A., McNeer, G. P. and Craver, L. F. Splenectomy in far-advanced Hodgkin's disease, *Blood 9*:824-36, 1954.
15. Ellison, R. R. Management of acute leukemia in adults, *Med. Clin. N. Amer. 40*:743-59, (May) 1956.
16. Krumbhaar, E. B. Leukemoid blood pictures in various clinical conditions, *Amer. J. med. Sci. 172*:519-33, 1926.
17. Personal unpublished observations.
18. Bichel, J. Lymphatic leukemia and lymphatic leukemoid states in cancer of the stomach, *Blood 4*:759-66, 1949.
19. Lee, Stanley L. Personal communication.
20. Valentine, W. N. and Beck, W. S. Biochemical studies on leucocytes. I. Phosphatase activity in health, leucocytosis and myelocytic leukemia, *J. Lab. clin. Med. 38*:39-55, 1951.
21. Wiltshaw, E. and Moloney, W. C. Histochemical and biochemical studies on leukocyte alkaline phosphatase activity, *Blood 10*:1120-31, 1955.
22. Hirsch, E. O. and Gardner, F. H. The transfusion of human blood platelets, *J. Lab. clin. Med. 39*:556-69, 1952.
23. Klein, E. and others. The preparation and clinical administration of lyophilized platelet material to children with acute leukemia and aplastic anemia, *J. Pediat. 49*:517-22, 1956.
24. Stefanini, M., Magalini, I. and Patterson, J. M. The relation of neoplastic tissue antigens to "autoimmune" hematologic syndromes (abstract), *Clin. Res. Proc. 4*:82, 1956.
25. Harrington, W. J. Hepatomegaly, splenomegaly and purpura, *Amer. J. Med. 21*:442-49, 1956.

METABOLIC DISTURBANCES IN DISSEMINATED NEOPLASTIC DISEASE*†

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Metabolism has been defined as tissue change and as such it is a term which can be applied to all the chemical functions of a cell. It is not my intention to review the metabolism of a cancer cell but rather to discuss certain biochemical alterations, occurring in the course of disseminated cancer, which lead to clinical symptoms and signs. My objectives are to indicate the broad scope of these disturbances and to illustrate how some can be managed. Points concerning management are offered in the belief that a physician discharges his fullest duty to his patient only when he undertakes to alleviate his patient's problems, regardless of the fact that a particular situation may be ultimately fatal.

A general classification is shown in Table I. The presence of tumor in an organ system may obviously lead to deranged function by interfering with the normal physiological processes of that system. Metabolic disturbances may arise also as a result of the action of substances produced by tumors or as a result of the rapid anabolism and catabolism of tumor tissue. Finally, owing to the more aggressive therapeutic approach to the problems of disseminated cancer, metabolic disturbances may result from treatment.

Some of the disturbances which result from disruption of organ systems by tumor are outlined in Table II. *Hypoproteinemia* and *defective hepatic glycogenesis* have been described in patients with gastric carcinoma and restoration of plasma protein levels to normal was found not to occur despite establishment of a positive nitrogen balance.[1] The mechanisms underlying these changes are unknown.

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TABLE I.—METABOLIC DISTURBANCES IN NEOPLASTIC DISEASE

1. Those related to the presence of tumor in certain organ systems.
2. Those produced by substances which have been elaborated by tumors.
3. Those related to the rapid anabolism and catabolism of tumor tissue.
4. Those related to the treatment of neoplastic disease.

TABLE II.—SOME DISTURBANCES RELATED TO THE PRESENCE OF TUMORS IN ORGAN SYSTEMS

GI tract: Hypoproteinemia; hypokalemic alkalosis
Liver: Liver coma; hypoglycemia; ammonia intoxication
Lung: Anoxemia; respiratory acidosis
Skeleton: Hypercalcemia with hyper- or hypophosphatemia
GU tract: Renal acidosis; nephrotic syndrome
CNS: Respiratory acid-base disturbances; hypernatremia
Endocrine: Adrenal insufficiency; diabetes insipidus
General: "Third-space" effects; "Dissolution syndrome"

Whether the tumor disrupts some metabolic activity of the stomach thus causing hypoproteinemia or whether these effects are mediated through altered liver or adrenal function or through some other mechanism cannot be stated. The *electrolyte disturbances* of disseminated cancer involving the gastrointestinal tract are most commonly the hypochloremic, hypopotassemic alkalosis of high intestinal obstruction and the metabolic acidosis of excessive small intestinal losses. Intraperitoneal seeding of tumor may lead to ascites formation with expansion of the extracellular space into a sequestered fluid collection, a so-called "*third space*".[2] We have observed a patient with vesico-rectal fistula who developed *hyperchloremic acidosis* which appeared to be due to pooling of urine in the sigmoid in a fashion similar to what may be seen in ureterosigmoidostomy.[3, 4]

Hypoglycemia has been observed as a feature both of primary and metastatic disease of the liver and with malignant spindle cell tumors.[5, 6] A recent report[7] described a patient who was brought into the hospital in coma and hypoglycemia was suspected when the cerebrospinal fluid

sugar was found to be low. Hypoglycemia was confirmed and was found to be responsive but later unresponsive to dextrose infusions. At postmortem examination an extensive hepatoma was discovered. A low cerebrospinal fluid sugar may not necessarily indicate hypoglycemia but rather may be a sign of meningeal metastases.[8] This may initially cause confusion with more well-known causes of lowered cerebrospinal fluid sugar such as bacterial and tuberculous meningitis.

Coma in patients with liver failure may be due to an *elevation of blood ammonia* and such patients have been found to have *respiratory alkalosis* in the early phases of ammonia intoxication.[9] Treatment measures include oral antibiotics,[10] frequent enemas to reduce ammonia production, sodium glutamate, and more recently arginine, by vein to decrease the circulating ammonia.[11, 12]

The phenomenon of *hypercalcemia* may result when the rate of growth of tumor in bone is such that calcium enters the blood stream at a rate which exceeds the ability of the kidneys to clear it.[13, 14] Rarely hypercalcemia may occur without detectable bone disease.[15] One example of this will be considered shortly.

Renal failure with metabolic acidosis is usually encountered in patients with pelvic tumors obstructing both ureters. Although the immediate management is similar to the treatment of renal acidosis from any cause, relief of the underlying ureteral obstruction is essential and can be achieved in some patients by roentgen therapy to the pelvic tumor whereas nephrostomy may have to be done in others. In some instances intra-arterial nitrogen mustard[16] has been used to cause regression of pelvic tumors. An intra-arterial catheter is introduced in a retrograde fashion into the lower abdominal aorta via the femoral artery and the appropriate dose of nitrogen mustard is delivered through the catheter. This technique permits the maximum effect to be delivered to the area under treatment.

Rarely, the *nephrotic syndrome* may be encountered as a result of renal amyloidosis seen at times in association with Hodgkin's disease and multiple myeloma.[17, 18] The nephrotic syndrome may occur also as a result of bilateral renal vein thrombosis[19, 20] secondary to multiple thromboses and, although no reports have been encountered by us, the syndrome might conceivably result from compression of the renal veins by the tumor.

The various electrolyte abnormalities listed under the central nerv-

ous system and pulmonary system (Table II) are well established. In addition to the *respiratory acid-base changes* which may be seen in central nervous system lesions, *hypernatremia* has been described in such patients (without evidence of diabetes insipidus) and renal wastage of salt has also been observed.[21] Extensive intrapulmonary metastases may impair exchange of respiratory gases with resultant *alveolar respiratory insufficiency*.[22] We have observed a patient who had reticulum cell sarcoma of the lungs and *respiratory acidosis* which was temporarily relieved after the administration of nitrogen mustard.[23]

Involvement of endocrine organs may lead to insufficiency of the organ concerned although the mere presence of tumor does not necessarily indicate that an endocrine gland will be functionally inadequate. Although carcinomas (particularly of the lung) often metastasize to the adrenals, actual clinical symptomatology of *adrenal failure* is difficult to distinguish from the total picture of deterioration. The use of adrenal steroids as replacement therapy is often tried but with little success. *Diabetes insipidus* has been described as a result of pituitary metastases but this is a rare phenomenon. In a recent report only six necropsy-proven cases could be found in the literature over a period of 30 years.[24]

Some terminally ill patients demonstrate general electrolyte abnormalities which appear to be indicative of impending dissolution. This "*dissolution syndrome*" is usually characterized in our experience by a falling serum sodium, a rising serum potassium and over-expansion of the extracellular space, and is presumably related to altered cell membrane permeability. Rubin and co-workers[25] reported that in a group of 78 seriously ill patients the measured plasma osmolality exceeded by 40-125 milliosmols per kilogram of water the calculated value. Ninety-eight per cent of these patients died within two weeks after the finding of hyperosmolality. The changes are non-specific, however, and may be seen in any long-standing illness near its termination.

Thus far we have considered briefly the numerous metabolic disturbances which may arise as a consequence of the presence of tumor in certain organs. Figure 1 illustrates the management of one such disturbance, hypercalcemia, in a patient with lymphosarcoma. At a time when this patient was comatose owing to hypercalcemia, she was given nitrogen mustard 0.3 mg./kg. intravenously. There followed

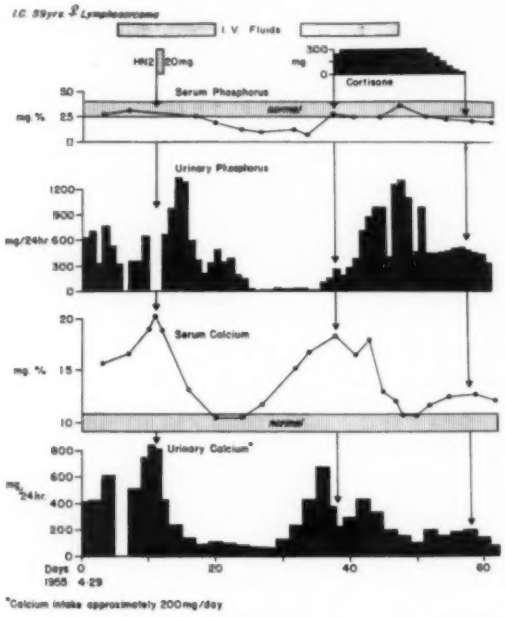

Figure 1.—Calcium and phosphorus levels in the serum and urine in a patient with lymphosarcoma treated with nitrogen mustard and cortisone.

a rapid decrease in the serum and urinary calcium levels to normal. The patient gradually regained consciousness and improved sufficiently to be up in a wheelchair and to eat a regular diet again. The hypercalcemia soon recurred, however, and on this second occasion reversal of these changes was accomplished by treatment with cortisone. The hypophosphatemia, hypercalcemia and hypercalcuria raised the possibility of an independent hyperparathyroidism but a subsequent postmortem examination revealed normal parathyroid glands. Although serum phosphorus levels have been reported to be slightly higher than normal in patients with disseminated bone cancer,[13] in our recent experience the level of phosphorus in the blood may be high or low in such situations and has not been of much help in differentiating hypercalcemia of malignant bone disease from that due to other causes. An additional finding of interest was that bone marrow invasion by tumor could not

TABLE III.

L. D., 33, Negress

July 1953: Radical hysterectomy for carcinoma of the cervix.
August 1953: Calcific shadow right kidney; right hydronephrosis.
August 1953-July 1955: Recurrent pyelonephritis.
July 1955: Admitted for pyelonephritis and polyuria.

Blood sugar 294 mg.%	*Skeletal survey:* demineralization
Serum calcium 15.5 mg.%	*Serum protein* 9.0 gm.% *Albumin* 4.5 gm.%
Serum phosphorus 2.7 mg.%	*Cephalin flocculation* ++++ *BSP* 30%
Urinary calcium 176 mg./24 hrs.	*Hemoglobin* 7.6 gm.%
Alkaline phosphatase 11.7 Bodansky Units	*Marrow:* hypocellular *BUN* 18.2 mg.%

Differential diagnosis
Hyperparathyroidism
Osseous metastases with hypercalcemia
Myeloma with hypercalcemia
Sarcoidosis with hypercalcemia

be demonstrated either by roentgen survey of the skeleton, by bone marrow aspirations during life or by examination of the bones at autopsy. Bone metastases can be demonstrated in the great majority of instances of hypercalcemia in malignant disease but there are a few instances in which they cannot.[15] The mechanism of such hypercalcemia remains unknown, although it has been postulated that some tumors may secrete a bone-resorbing substance.[26] Although nitrogen mustard and cortisone have been used most often in the management of hypercalcemia in disseminated cancer, a new antimetabolite, 6-diazo-5-oxo-L-norleucine (DON) has also proved useful in the treatment of this complication.[27]

The metabolic complexities which can arise in patients with cancer are outlined in Table III which summarizes the pertinent clinical information in a patient with carcinoma of the cervix. Although definite dissemination of this patient's disease could not be demonstrated conclusively, such was suspected because of anemia, hepatomegaly, abnormal liver function and hydronephrosis. When the polyuria, which was attributed to diabetes mellitus, did not fully subside with insulin administration other causes for polyuria were investigated. Findings compatible with hyperparathyroidism were noted but in addition the other laboratory data made tenable any one of the four diagnoses listed. The

TABLE IV.—PRIMARY SITES OF FUNCTIONING TUMORS AND SOME DISTURBANCES WHICH THEY PRODUCE

Pituitary	Cushing's
Thyroid	Hyperthyroidism
Parathyroids	Hyperparathyroidism
Adrenals	Cushing's; pheochromocytoma; aldosteronism
Pancreas	Hyperinsulinism
Gonads	Masculinizing and feminizing syndromes
Miscellaneous	Malignant carcinoid; dysproteinemias

possibility of osseous metastases could not be substantiated by bone marrow aspiration, and the skeletal survey revealed minimal but generalized demineralization rather than lytic lesions. The anemia was regarded as probably secondary to long-standing renal disease and chronic infection although anemia has been noted in patients with hyperparathyroidism with extensive osteitis fibrosa.[28] Inasmuch as there was no Bence-Jones proteinuria and no myeloma cells were noted on marrow aspiration the possibility of multiple myeloma was excluded. An electrophoretic study of the serum proteins revealed an increase in a_2 globulin but no spike configuration of gamma globulin typical of myeloma protein. The clinical and laboratory findings were compatible with sarcoidosis but there was no peripheral or hilar lymphadenopathy and no skin or bone lesions suggestive of sarcoidosis. The patient was accordingly explored and a parathyroid adenoma was found in the left retroclavicular region. She recovered and remained well until a year later when she succumbed to widespread cancer. This case serves as a reminder that although metabolic disturbances may arise as a consequence of disseminated cancer, coincidental but unrelated metabolic diseases may occur to confound the clinician.

Some of the disturbances of neoplasms of endocrine organs produced by virtue of the hormonal substances elaborated are shown in Table IV. By far the great majority of these disturbances are caused by hyperfunctioning adenomas but there are, however, a small number of instances of disseminated hyperfunctioning malignant tumors of endocrine origin. *Cushing's syndrome* may result from metastatic carcinoma of the basophil cells of the pituitary[29] but this is rare compared

to adrenocortical carcinoma as a cause of this disorder. When Cushing's syndrome occurs as a result of metastatic carcinoma, there is little to offer the patient, although recent studies with amphenone B,[30] which apparently specifically inhibits the synthesis of biologically active 17-hydroxycorticoids, hold promise for treatment of such patients in the future. Patients with *hyperthyroidism* due to cancer of the thyroid with functioning metastases can be restored to a euthyroid state by treatment with thiouracil and radioiodine.[31] Carcinomas of the parathyroids are rare, only one case in more than 100 cases of *hyperparathyroidism* having been observed by Black at the Mayo Clinic.[32] Treatment consists in removing as much hyperfunctioning tissue as possible if the disease is locally extensive. If disseminated, there is no known effective measure, although a parahormone inhibitor would be of theoretical value if such existed.

Functioning malignant *pheochromocytomas* have been reported[33] and Regitine offers a possible approach to therapy in controlling the hypertension of disseminated tumors of this origin. The syndrome of primary aldosteronism recently described by Conn[34, 35] is usually associated with adrenocortical adenoma but has also been found to occur with adrenal cortical carcinoma.[36] The first surgically proven case of *hyperinsulinism* was a carcinoma of the islet cells with liver metastases.[37] In a review by Crain and Thorn[38] about 10 per cent of 258 cases of hyperinsulinism were due to metastatic carcinoma of the islet cells. Although alloxan is of theoretical value in such cases, practically speaking it has proved to be too toxic for clinical use.[6, 38] *Masculinizing* and *feminizing syndromes* are well-known examples of disturbances produced by substances elaborated by tumors. Although such syndromes are frequently adrenal in origin, gonadal causes must always be considered.[39, 40]

One of the most exciting chapters in the field of hyperfunctioning tumors has been written recently with the description of a clinical syndrome due to *malignant carcinoid*.[41, 42] Apparently most cases have liver metastases although these are said to be non-essential for the production of the syndrome. The clinical findings consist of vasomotor disturbances (usually cyanosis and flushing), chronic diarrhea, asthmatic-like respiratory symptoms and valvular disease of the right side of the heart. These changes are thought to result from serotonin which is secreted by the tumor. Sjoerdsma, Weissbach and Uden-

TABLE V.—SOME DISTURBANCES RELATED TO THE RAPID ANABOLISM AND CATABOLISM OF TUMOR TISSUE

Lymphomas and leukemias — Uric acid lithiasis
Leukemia — Elevated basal metabolism
General — Weight loss, malnutrition, fever

friend[41] found that whereas normally only about one per cent of dietary tryptophan is metabolized to serotonin, in patients with malignant carcinoid as much as 60 per cent of ingested tryptophan is converted to serotonin, thus demonstrating an abnormal diversion presumably as a result of the metabolic activity of the tumor.

The *dysproteinemias* include the increasingly complex protein disturbances of multiple myeloma[43] as well as cryo- and macroglobulinemia.[44, 45] Some of these proteins may lead to disturbances such as bleeding, purpura, and Raynaud's phenomenon.

Disturbances due to *rapid turnover of tumor tissue* are summarized in Table V. Since rate of change is important in the production of some of these disturbances it is not unexpected that they occur chiefly in the lymphomatous diseases, where marked changes in tumor growth may occur spontaneously (or as a result of treatment) in relatively short periods of time. *Uric acid lithiasis*, although more often seen as a complication of therapy[40, 47] may occur spontaneously. There are no known effective measures in treatment other than to enhance the solubility of uric acid by making the urine alkaline and to ensure that the patient's fluid intake and output is plentiful. Ureteral irrigation may occasionally be of help when there has been extensive crystallization in the ureters. Since uric acid may be dialyzed, the use of an artificial kidney should be considered in situations of renal shutdown due to uric acid lithiasis. It has been suggested that uricosuric agents be used prior to radiotherapy in patients with hyperuricemia.[47] However, we feel the use of these agents should be avoided, since in the majority of instances the problem is not one of diminished renal clearance, but one of a marked increase in uric acid excretion accompanied by uric acid crystallization in the kidneys and ureters. One possible exception is their cautious use in pre-treatment periods if the elevated blood

TABLE VI.—TREATMENT OF NEOPLASTIC DISEASE AND SOME DISTURBANCES RELATED TO IT

Surgery:	Dumping syndrome (gastrectomy)
	Hypoparathyroidism (radical neck dissection)
	Myxedema (hypophysectomy or radical neck dissection)
	Diabetes insipidus (hypophysectomy)
	Adrenal insufficiency (hypophysectomy or adrenalectomy)
	Hyperchloremic acidosis (ureterosigmoidostomy)
	Diabetes mellitus (total pancreatectomy)
Radiation therapy and Chemotherapy:	Electrolyte abnormalities
	Uric acid lithiasis
Sex Steroids:	Hypercalcemia
	Salt retention with edema
Adrenal Steroids:	Cushing's
	Steroid diabetes
	Hypokalemia

uric acid is associated with a low urinary uric acid and measures such as fluids and alkalinization have failed to correct the hyperuricemia.

The *elevated basal metabolism* seen in some patients with acute leukemia has been recognized for many years. The mechanism has been related to increased oxygen utilization by leukemic cells by some investigators while others have felt this to be an inadequate explanation and have related the change to a marked increase in nitrogen catabolism.[48] Whatever the exact cause, the elevated metabolic rate, fever and tachycardia return to normal when a remission is induced. The *weight loss and malnutrition* of disseminated cancer are associated with a negative nitrogen balance but exactly what triggers the series of changes leading to these abnormalities is not clear. Their inclusion under the general topic of anabolism and catabolism is not meant to imply that they are due to rapid turnover of tumor tissue per se but rather to mean that weight loss and malnutrition are complex metabolic disturbances which may result from cancer growth even though specific disruption of a vital organ system cannot be demonstrated.[49] It has been reported[50] that once a negative nitrogen balance is established it is very difficult to re-establish a positive nitrogen balance since in these patients nitrogen losses are further stimulated by increasing the intake. This

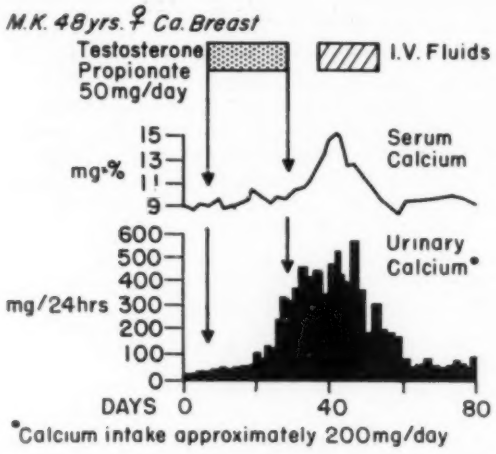

Figure 2.—Serum and urinary calcium data in a patient with metastatic mammary carcinoma under treatment with testosterone propionate. (Reprinted, by permission, from Myers, W. P. L. Medical Clinics of North America 40:871-885, 1956, ref. 14.)

is true up to a point beyond which retention may be achieved but the intakes required are usually far in excess of what is necessary to achieve a positive nitrogen balance in normals.[50]

The final category of disturbances, namely those related to the treatment of disseminated cancer, is outlined in Table VI. Various surgical procedures including gastrectomy, hypophysectomy, adrenalectomy and ureterosigmoidostomy may lead, respectively, to the *dumping syndrome, diabetes insipidus, myxedema, adrenal insufficiency* and *hyperchloremic acidosis*. The management of these situations has been extensively reviewed[3, 4, 51-53] and will not be reviewed here. It need hardly be emphasized, however, that the management of these metabolic disturbances should be thoroughly understood when these surgical procedures are employed. *Myxedema* and *hypoparathyroidism* following radical neck dissections for thyroid carcinoma pose no special problems in management although we have encountered a few hypoparathyroid patients with hypercalcemia secondary to *over-treatment with vitamin D*. The *diabetes mellitus* following total pancreatectomy is usually mild and readily controlled.

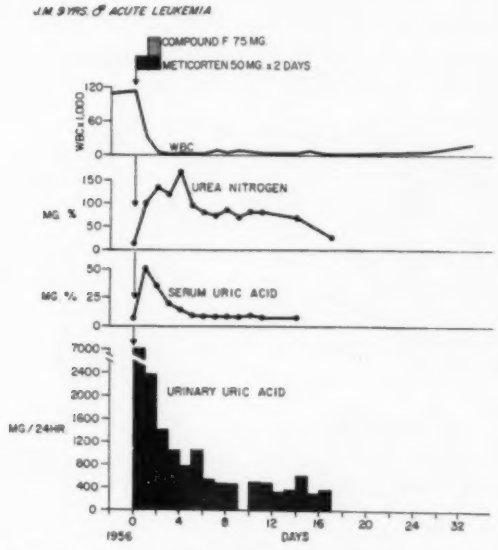

Figure 3.—Data on serum and urinary uric acid levels in a 9 year old boy with acute leukemia under treatment with adrenal steroids.

The use of drugs and radiation therapy in the treatment of disseminated cancer may induce a variety of disturbances including *electrolyte disorders, hyperuricemia,* and *functional abnormalities of the liver.* The serum and urinary uric acid changes induced by therapy in a young boy with acute leukemia are illustrated in Figure 2. After 50 mg. of Meticorten had been administered over a period of 12 hours, marked hyperuricemia developed accompanied by a huge output of uric acid in the urine. In addition there was a rise in the blood urea nitrogen to levels above 150 mg. per cent. Although renal shutdown secondary to uric acid lithiasis did not occur in this patient, it may occur following both chemotherapy and radiation therapy[46, 47] and hence represents a problem to be reckoned with, particularly in the treatment of lymphomas and leukemias. Patients undergoing treatment with radiation are also prone to develop a *negative nitrogen balance*[50] and weight loss and malnutrition may occur as a consequence.

In addition to *salt retention with edema* formation, *hypercalcemia*

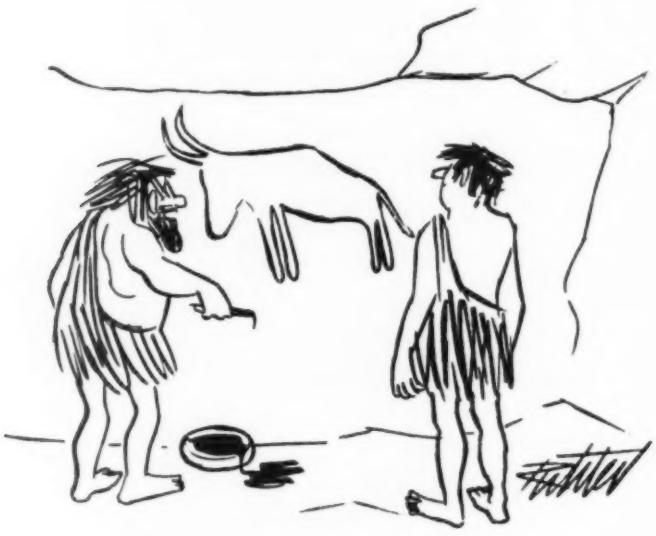

Figure 4.—*"Well, there you are, young fellow. I've taught you everything I know."*—Drawing by Richter.

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may result from the use of sex steroids.[54-56] This metabolic hazard may arise with both androgen and estrogen therapy and its occurrence with the former is illustrated in Figure 3. The rising urinary calcium, during a course of testosterone therapy for metastatic breast cancer, afforded an excellent guide to impending hypercalcemia and the steroid was stopped at a time when the patient was still normocalcemic. The serum calcium subsequently reached a peak of 15 mg. per cent two weeks after cessation of treatment apparently as a result of the delayed effects of the intramuscular therapy. Since hypercalcemia may be fatal it is important to be mindful of its possible occurrence during the treatment of disseminated breast cancer.

Cushing's syndrome is usually seen only with the prolonged use of adrenal steroids and yet the malignant disease under treatment often demands continuation of these hormones. Some control may be achieved by reduction in dosage and the use of androgens concomitantly for

their anabolic effect should be considered. "*Steroid diabetes*", which is characterized by insulin unresponsiveness, diminution in glycosuria with fasting and a negative nitrogen balance,[57] occurs infrequently but is nevertheless of sufficient importance to be watched for in all patients undergoing treatment with adrenal steroids. This is particularly true of those with a positive family history for diabetes. *Potassium deficiencies* are frequent with prolonged adrenal steroid therapy and supplementary potassium is usually necessary.

Figure 4 in all probability summarizes the content of this paper. I can only hope that the exposition of the material is as clear.

Summary: A review of some of the metabolic disturbances in disseminated cancer has been presented together with considerations regarding management.

Acknowledgments: I am indebted to Dr. Irwin H. Krakoff and Dr. Lois Murphy for making available to me the data shown in Figure 2 and to Dr. David Karnofsky whose faithful perusal of the literature led to the reproduction shown in Figure 4.

REFERENCES

1. Homburger, F. and others. Further studies on metabolic changes in patients with gastric cancer, *J. nat. Cancer Inst. 10*:489-491, 1949.
2. Randall, H. T. Water and electrolyte balance in surgery, *Surg. Clin. No. America 32*:445-69, 1952.
3. Ferris, D. O. and Odel, H. M. Electrolyte pattern of the blood after bilateral ureterosigmoidostomy, *J. Amer. med. Assoc. 142*:634-40, 1950.
4. Perry, F. A., Deddish, M. R., Randall, H. T. and Roberts, K. E. Evaluation of plasma electrolytes and renal function in patients with sigmoid urinary pouches, *Surg. Forum. 6*:599-603, 1956.
5. Conn, J. W. and Seltzer, H. S. Seminars on carbohydrate metabolism, *Amer. J. Med. 19*:460-78, 1955.
6. Porter, M. R. and Frantz, V. K. Tumors associated with hypoglycemia, pancreatic and extrapancreatic, *Amer. J. Med. 21*:944-61, 1956.
7. Khaira, B. S. Primary carcinoma of liver presenting as hypoglycaemia, *Brit. med. J. 1*:902-03, 1956.
8. Central nervous system disease characterized by low spinal fluid sugar, Clinico-pathologic conference, *Amer. J. Med. 20*:275-85, 1956.
9. Vanamee, P. and others. Respiratory alkalosis in hepatic coma, *A.M.A. Arch. intern. Med. 97*:762-67, 1956.
10. Fisher, C. J. and Faloon, W. W. Control of blood ammonia in cirrhosis by oral neomycin, *Clin. Res. Proc. 4*:147, 1956.
11. Roberts, K. E. and others. Electrolyte alterations in liver disease and hepatic coma, *Med. Clin. No. America. 40*:901-14, May 1956.
12. Najarian, J. S. and Harper, H. A. A clinical study of the effect of arginine on blood ammonia, *Amer. J. Med. 21*: 832-42, 1956.
13. Woodard, H. Q. Changes in blood chemistry associated with carcinoma metastatic to bone, *Cancer 6*:1219-27, 1953.
14. Myers, W. P. L. Clinical aspects and management of hypercalcemia, *Med. Clin. No. America, 40*:871-85, May 1956.
15. Plimpton, C. H. and Gellhorn, A. Hypercalcemia in malignant disease without evidence of bone destruction, *Amer.*

J. Med. 21:750-59, 1956.

16. Krakoff, I. H. Intra-arterial nitrogen mustard in the treatment of pelvic cancer. To be published.
17. Hoffman, G. T., Rottino, A. and Summerill, F. Genito-urinary tract lesions in Hodgkin's disease (abstract) *Bull. N. Y. Acad. Med. 29*:655-57, 1953.
18. Allen, A. C. *The kidney, medical and surgical diseases.* New York, Grune and Stratton, 1951
19. Pollak, V. E. and others. Renal vein thrombosis and the nephrotic syndrome, *Amer. J. Med. 21*:496-520, 1956.
20. Kaplan, B. M. and others. Bilateral renal vein thrombosis and the nephrotic syndrome, *Ann. intern. Med. 45*:505-18, 1956.
21. Welt, L. G. and others. Role of the central nervous system in metabolism of electrolytes and water, *A.M.A. Arch. intern. Med. 90*:355-78, 1952.
22. Baldwin, E. DeF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. II. A study of 39 cases of pulmonary fibrosis, *Medicine, 28*:1-25, 1949.
23. Karnofsky, D. A., Myers, W.P.L. and Phillips, R. Treatment of the inoperable pulmonary cancer, primary and metastatic, *Amer. J. Surg. 89*:526-37, 1955.
24. Peabody, H. D., Jr. and Olsen, A. M. Association of bronchogenic carcinoma and diabetes insipidus: Report of cases, *Proc. Mayo Clin. 26*:107-12, 1951.
25. Rubin, A. L. and others. The relationship between plasma osmolality and concentration in disease states, *Clin. Res. Proc. 4*:129, 1956.
26. Connor, T. B., Thomas, W. C., Jr. and Howard, J. E. The etiology of hypercalcemia associated with lung carcinoma (abstract), *J. clin. Invest. 25*:697-98, 1956.
27. Myers, W.P.L. and Magill, G. B. Alterations in calcium metabolism in cancer patients treated with 6-diazo-5-oxo-L-norleucine, *Proc. Soc. exp. Biol. Med. 93*:314-18, 1956.
28. Albright, F. and Reifenstein, E. C., Jr. *The parathyroid glands and metabolic bone disease.* Baltimore, Williams and Wilkins, 1948.
29. Sheldon, W. H., Golden, A. and Bondy, P. K. Cushing's syndrome produced by a pituitary basophil carcinoma with hepatic metastases, *Amer. J. Med. 17*: 134-42, 1954.
30. Thorn, G. W. and others. Inhibition of corticosteroid secretion by amphenone in a patient with adrenocortical carcinoma, *New Engl. J. Med. 254*:547-51, 1956.
31. Leiter, L., Seidlin, S. M., Marinelli, L. D. and Baumann, E. J. Adenocarcinoma of the thyroid with hyperthyroidism and functional metastases. I. Studies with thiouracil and radio-iodine, *J. clin. Endocrinol. 6*:247-61, 1946.
32. Black, B. M. *Hyperparathyroidism.* Springfield, Ill. Charles C. Thomas, 1953.
33. Tamura, P. Y. and Lawrence, L. T. Multiple tumors of the sympathetic system. A report of a case of malignant schwannoma associated with functioning malignant pheochromocytoma, *Cancer. 9*:293-99, 1956.
34. Conn, J. W. Presidential address. Part I. Painting background. Part II. Primary aldosteronism, a new clinical syndrome, *J. Lab. clin. Med. 45*:3-17, 1955.
35. Conn, J. W. Progress Report: Primary aldosteronism, *J. Lab. clin. Med. 45*: 661-64, 1955.
36. Foye, I. V., Jr. and Feichtmeir, T. V. Adrenal cortical carcinoma producing solely mineralocorticoid effect, *Amer. J. Med. 19*:966-75, 1955.
37. Wilder, R. M., Allan, F. M., Power, M. H. and Robertson, H. E. Carcinoma of the islands of the pancreas, hyperinsulinism and hypoglycemia, *J. Amer. med. Assoc. 89*:348-55, 1927.
38. Crain, E. L., Jr. and Thorn, G. W. Functioning pancreatic islet cell adenomas, *Medicine 28*:427-47, 1949.
39. Javert, C. T. and Finn, W. F. Arrhenoblastoma. The incidence of malignancy and the relationship to pregnancy, sterility and to treatment, *Cancer 4*:60-77, 1951.
40. Teilum, G. Estrogen-producing Sertoli

cell tumors (androblastoma tubulare lipoides) of the human testis and ovary; Homologous ovarian and testicular tumors. III, *J. clin. Endocrinol. 9*:301-18, 1949.

41. Sjoerdsma, A., Weissbach, H. and Udenfriend, S. A clinical physiologic and biochemical study of patients with malignant carcinoid (argentaffinoma), *Amer. J. Med. 20*:520-32, 1956.
42. Eyler, W. R., Tesluk, H. and Drake, E. H. Malignant argentaffinoma associated with cardiovascular abnormalities, *New Engl. J. Med. 254*:555-59, 1956.
43. Osserman, E. F. and Lawlor, D. P. Abnormal serum and urine proteins in thirty-five cases of multiple myeloma, as studied by filter paper electrophoresis, *Amer. J. Med. 18*:462-76, 1955.
44. Wilde, H. and Hitzelberger, A. L. Macroglobulinemia. Clinical features and differential diagnosis, *Blood 9*:875-80, 1954.
45. Mackay, I. R., Eriksen, N., Motulsky, A. G. and Volwiler, W. Cryo- and macroglobulinemia. Electrophoretic, ultracentrifugal and clinical studies, *Amer. J. Med. 20*:564-87, 1956.
46. Kravitz, S. C., Diamond, H. D. and Craver, L. F. Uremia complicating leukemia chemotherapy. Report of a case treated with triethylene melamine, *J. Amer. med. Assoc. 146*:1595-97, 1951.
47. Merrill, D. Uremia following x-ray therapy in leukemia, *New Engl. J. Med. 222*:94-97, 1940.
48. Forkner, C. E. *Leukemia and allied disorders*. New York, The MacMillan Co., 1938.
49. Mider, G. B. Some aspects of nitrogen and energy metabolism in cancerous subjects: A review, *Cancer Res. 11*:821-29, 1951.
50. Bolker, N. Nitrogen balance in malignant disease, *Amer. J. Roentgenol. 69:* 839-48, 1953.
51. Roberts, K. E., Randall, H. T., Bane, H. N., Medwid, A. and Schwartz, M. K. Studies of the physiology of the dumping syndrome, *N. Y. State J. Med. 55:* 2897-2902, 1955.
52. Lipsett, M. B. and Pearson, O. H. Effects of hypophysectomy in man, *Med. Clin. No. America. 40*:773-86, 1956.
53. Lipsett, M. B., Li, M. C., and Pearson, O. H. Medical management of adrenalectomy and hypophysectomy, *A.M.A. Arch. intern. Med. 97*:634-38, 1956.
54. Farrow, J. H. and Woodard, H. Q. The influence of androgenic and estrogenic substances on the serum calcium in cases of skeletal metastases from mammary cancer, *J. Amer. med. Assoc. 118*:339-43, 1942.
55. Herrmann, J. B., Adair, F. E. and Woodard, H. Q. The use of testosterone propionate in the treatment of advanced carcinoma of the breast: II. The treatment of osseous metastases, *Surgery 22:* 101-19, 1947.
56. Myers, W. P. L., West, C. D., Pearson, O. H. and Karnofsky, D. A. Androgen-induced exacerbation of breast cancer measured by calcium excretion; conversion of androgen to estrogen as a possible underlying mechanism, *J. Amer. med. Assoc. 161*:127-31, 1956.
57. Sprague, R. G. Steroid diabetes (editorial), *Diabetes 2*:159, 1953.

MANAGEMENT OF DISSEMINATED NEOPLASTIC DISEASE: THE DIRECT EFFECTS OF CANCER*

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TO discuss in a concise but comprehensive manner the therapeutic management of problems resulting directly from cancer is a formidable task which can be approached only through the aid of generalization and outlines. Accordingly this presentation will be based on a group of maxims concerning incurable cancer, an outline of the mechanisms by which cancer can directly cause pathology, a schema to guide the choice of therapy, a few examples of specific problems in palliative treatment, and some statistics to indicate the magnitude and present status of this clinical problem. It must constantly be remembered that this discussion refers to incurable cancer only.

Figure 1 presents five maxims concerning incurable cancer. These may be over-simplified or over-dramatic, but they merit careful consideration, and will serve to orient this discussion. *Cancer is not A disease.* Cancer is many diseases, having certain characteristics in common, but presenting as great a diversity in other characteristics as do the various infectious diseases. *Incurable cancer is not a diagnosis.* It is not a diagnosis which is adequate to form the basis of rational palliative therapy. Precise diagnosis of the immediate causes of incapacity is of the greatest practical importance in incurable cancer, for when it becomes impossible to eradicate a disease it becomes increasingly important to attack the immediate site of pathogenesis.

No tissue is spared by cancer. There is no member of the body, no system, no organ, no tissue, in fact no cell but may give rise to or become affected by cancer. In spite of this diversity *cancer is not mysterious.* The basic mechanisms of cancer pathogenesis are disruptions of normal anatomy and physiology. With a knowledge of the

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MAXIMS CONCERNING INCURABLE CANCER

Cancer is Not *A* Disease

Incurable Cancer is Not a Diagnosis

No Tissue is Spared by Cancer

Cancer is Diverse But Not Mysterious

Cancer Doesn't Matter if the Patient isn't Sick

Figure 1

DIRECT EFFECTS OF CANCER

Mechanisms	*Examples*
I. Malfunction of tissue or origin	
A. Hyperfunction	Cushing's Syndrome, Serotonin Syndrome, Hyperproteinemia of Myeloma, Polycythemia Vera
B. Hypofunction	Leukemic Pancytopenia Anergy of Lymphoma
II. Mechanical Damage to other tissues	
A. Due to pressure (Mass)	CNS, GI, GU, Bronchi, Vessels, Bile Ducts
B. Due to infiltration	
1. Disruption	Liver, Kidney, Myocardium
2. Weakening	Arteries, GI, Fistulae, Bone,
3. Surface effects	Skin, Alveoli, Serosae

Figure 2—An outline of the mechanisms by which cancer is the direct cause of pathology.

natural history of each type of cancer and with modern diagnostic facilities these mechanisms can often be dissected and occasionally corrected.

The last maxim is *cancer doesn't matter if the patient isn't sick*. This statement would be tragically untrue if applied to curable cancer but once the possibility of complete eradication of cancer no longer exists it is well to remember that the existence of neoplastic cells within the body does not necessarily cause symptomatology. Hence it is wise to conserve our present inadequate armamentarium of therapeutic weapons

for the attack on those areas of neoplastic tissue which are actually causing disease.

Figure 2 presents a classification of the mechanisms by which cancer may be a direct cause of pathology. These mechanisms fall into two groups: malfunction of the tissue which has become neoplastic, and mechanical damage to non-neoplastic tissues caused by the excessive growth of the cancer. Problems of hyperfunction and hypofunction have already been discussed by the previous speakers[1-3] and will not be considered further here. Mechanical damage can occur both from pressure of a tumor mass upon normal structures or by disturbance of normal structures by infiltration of strands and nodules of tumor tissue. Obviously these mechanisms are not mutually exclusive. Nevertheless if one approaches these complex problems by analysis of the predominant pathological mechanisms, it will often be possible to give more successful palliative treatment or at least to better understand and better prognosticate the course of disease.

Pressure due to mass causes problems principally when it blocks flow through tubular organ systems–as in uremia due to obstruction of ureters, jaundice from blockage of the extrahepatic biliary ducts, esophageal or intestinal obstruction, and respiratory and vascular blockage as in the superior vena caval syndrome. A similar mechanism causes paraplegia due to cord compression.

Infiltration is a more complex mechanism which might be considered in three subcategories: disruption, weakness, and interference with surface functions. Disruption refers to damage to the internal structure of organs such as liver, kidney or myocardium (see case 4). Weakening results from the replacement or displacement of normal tissues of high tensile strength by cancer tissue which characteristically is noncohesive and often necrotic. This results in the arterial blowouts which are often the terminal episode in epidermoid carcinoma of the head and neck, perforations of the gastrointestinal tract as in lymphoma, and the fistula formation so common in pelvic cancers. Interference with surface functions occurs in several areas–cancer implants on serosal surfaces increase their permeability and hence cause effusions, widespread infiltration of skin such as occurs in mycosis fungoides causes loss of serous fluids and interferes with both diffusion and conservation of body heat, and a similar mechanism may impair the diffusion of oxygen and carbon dioxide across the alveolar membrane in diffuse infiltration

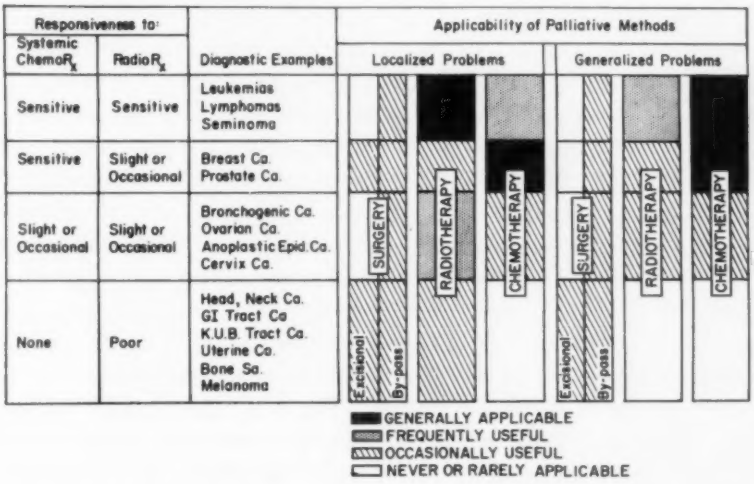

Figure 3—A schema to guide the choice of palliative procedures in incurable cancer. This concerns only methods of treatment aimed directly at the cancer. It does not consider treatment of indirect or incidental complications of cancer. "Chemotherapy" refers to antineoplastic drugs.

of the pulmonary parenchyma.

When palliative treatment does become necessary it should be given promptly and adequately to alleviate symptoms and forestall impending complications with a minimum of iatrogenic trauma and toxicity. To accomplish this demands of the physician—be he cancer specialist or general practitioner—a constant alertness to the dynamics of progressive cancer, a never-ceasing re-diagnosis and re-evaluation of pathogenic mechanisms, a familiarity with the natural history of each kind of cancer, and an awareness of available methods of therapy and their applicability to cancer of various types and in various locations. Figure 3 is an attempt to schematize such an approach to the management of incurable cancer.

With the histologic diagnosis established and the possibility of curative treatment ruled out, the first consideration is the probable responsiveness of this type of cancer to presently available therapeutic methods. All neoplasms may be considered responsive to palliative surgery if anatomically approachable, but responsiveness to ionizing

irradiations and systemic chemotherapy varies greatly. The four horizontal divisions of Figure 3 are separated according to usual responsiveness to these two types of treatment. The diagnostic examples are listed with considerable reservation, for great individual variation is expected in response to any type of treatment. The next step leading to a logical therapeutic decision is determination of the nature and extent of the *immediate problem*. This is not necessarily the total extent of disease, but only that particular part of the process which is currently making the patient sick or may soon do so. Thus a patient with a pelvic tumor mass causing bladder or ureteral obstruction has a local problem as regards immediate palliative treatment, even though he may also have distant metastases. A Hodgkin's disease patient with para-aortic adenopathy has multiple immediate problems because of the threat of mediastinal, ureteral, and intestinal obstruction. This might be approached therapeutically as a generalized problem or as multiple local problems. A patient with anemia due to neoplastic invasion of the bone marrow has a generalized problem.

The vertical bars in Figure 3 indicate the general applicability of therapeutic methods according to these several considerations. In those diseases such as the lymphomas and the chronic leukemias which are usually sensitive to both radiotherapy and chemotherapy (polyfunctional alkylating agents such as nitrogen mustard) radiotherapy is generally the treatment of choice if the offending lesion is localized, but chemotherapy is indicated if the immediate problems are multiple or generalized. Since both types of treatment are effective and neither is completely satisfactory, the decision as to treatment is often influenced by such factors as rapidity of effect, convenience, expense, and the experience of the physician, in addition to the location and extent of pathology. Surgery of the excisional type is rarely indicated in these diseases, but the surgeon is sometimes called on to re-establish anatomical or functional continuity (indicated as "By-pass surgery" in the figure) in such problems as intestinal perforation or urinary tract obstruction.

Cancer of the breast and prostate often respond to hormonal chemotherapy and are less often radiosensitive, so chemotherapy is often used even for localized problems, with radiotherapy and excisional surgery applicable to selected problems. For example, radiotherapy might be used for brain metastases, or for painful bone lesions not responding to hormonal therapy, and excisional surgery (*e.g.*, simple

mastectomy) might be the most effective treatment for a foul fungating local lesion.

There is a large group of cancers which cannot be classified as sensitive to either radiotherapy or chemotherapy, but which will respond well in occasional individuals or will usually respond slightly. When the necessity for treatment arises such cases should receive radiotherapy as the principle agent for localized problems but often a combination of radiotherapy and chemotherapy is advantageous. Treatment is indicated in such cases in spite of the poor expected response because sometimes even a little tumor shrinkage will afford symptomatic relief. This is especially true of lesions causing dyspnea, intestinal obstruction, and cord compression.

Finally there remains a distressingly large group of diagnoses (which includes the great majority of cancer patients) which is completely non-responsive to presently available chemotherapeutic agents and resistant to x-ray therapy. For these, excisional surgical procedures are occasionally palliative and the by-passing type of procedures such as colostomy, gastrojejunostomy, nephrostomy, and tracheostomy may be justified. It should also be remembered that even the most resistant tissue can be damaged by intensive radiotherapy and thus a neoplastic mass which is causing trouble may logically be treated by carefully directed radiotherapy regardless of its radioresistance.

Three examples of mechanical damage by cancer deserve special consideration as medical emergencies which can often be significantly benefited if promptly recognized and treated, and as illustrations of the several factors which determine choice of treatment.

Mediastinal tumor is most commonly due to lymphoma or bronchogenic carcinoma. Since it is a local problem but generally inaccessible to surgery, the indicated treatment is roentgen therapy in a dosage which will give prolonged suppression of tumor growth. However if intensive radiotherapy has previously been given into the area with actual or threatened fibrosis, or if it is impossible to make the differential diagnosis between tumor activity and fibrosis as the immediate cause of symptoms, a chemotherapeutic agent such as nitrogen mustard should be used instead of x-ray since this will not increase the fibrosis and may aid in the differential diagnosis as well as provide palliation. If a tumor is causing superior vena caval compression and bronchial obstruction, it demands prompt shrinkage and continued control, which

can best be accomplished by a combination of chemotherapy and radiotherapy. At present the chemotherapeutic agent of choice is usually HN2 administered in a single intravenous dose of 0.4 milligrams per kilogram of body weight. However, if the patient is in such severe dyspnea that asphyxia seems imminent, it seems logical to choose a drug which does not cause vomiting. In such case the best drug now available is intravenous triethylene melamine (TEM) given in doses of 2 to 3 milligrams at 24 hour intervals to a total dose of 0.15 milligrams per kilogram. This procedure rapidly initiates tumor shrinkage, without the danger of tissue edema which often follows x-ray treatment. It also permits more rapid subsequent treatment with x-ray than would otherwise be possible. Radiotherapy should then continue to full dosage—usually 2500r to 3500r tumor dose.

Spinal cord compression with resulting paraplegia achieves tremendous importance as a problem in inoperable cancer, not so much because it may cause death, but rather because the patient may continue to live in almost unbearable incapacity. A patient who has a fairly good prognosis for survival may develop metastases which cause paraplegia. He may then face months or years of paralysis without incapacitating trouble in any other area. The mechanism of paraplegia due to metastatic cancer is usually an epidural mass, or an infiltrative lesion in bone causing collapse of the vertebral column. It is almost never a lesion within the substance of the cord. The therapeutic necessity is immediate decompression. Laminectomy is the logical treatment for a radioresistant tumor, for an undiagnosed lesion, or for vertebral collapse. Laminectomy should be followed by radiotherapy. Nitrogen mustard followed immediately by radiotherapy is the treatment of choice for sensitive tumors such as Hodgkin's disease, and the experience of the past few years at Memorial Hospital indicates that this method is often effective even for epidermoid cancers and adenocarcinomas. Therefore, if a cord lesion cannot be localized, if it covers too wide an area for surgical decompression, or if neurosurgical treatment is not immediately available, this medical therapy should be utilized regardless of histologic diagnosis. The purpose of HN2 here, as in the mediastinal syndrome, is to cause the most rapid possible anti-tumor effect and to eliminate the initial edema which may follow x-ray alone. It also seems possible, although there is as yet no proof, that this combined therapy has an additive or synergistic anti-cancer effect.

This third example is blockage of the urinary tract. This is another situation in which slight differences in tumor size produce abrupt changes in clinical status. Two mechanisms frequently cause the difficulty—a tumor at the bladder trigone compressing the urethral or the ureteral openings, or multiple areas of pressure along the course of the ureters. Complete anuria seldom occurs so the condition may be unsuspected, but apparently back pressure is increased sufficiently to reduce renal function and when uremia ensues it progresses rapidly. The former problem should be anticipated in any patient with carcinoma of pelvic origin, and the latter situation is frequently encountered in the lymphomas. Treatment with chemotherapeutic agents is contraindicated if ureteral blockage has progressed to the point of nitrogen retention or oliguria because of the danger of uric acid crystallization (see discussion by Dr. Myers[3]). Radiotherapy is the usual treatment of choice but temporary or permanent nephrostomy may be necessary and ureteral transplantation is occasionally practicable if the tumor is localized (see case 2).

The following case histories provide further illustration of the palliative management of incurable cancer.*

Case 1 illustrates permanent control of a potentially incapacitating cord compression syndrome, and a later urological problem which proved to be curable and unrelated to the neoplastic disease.

A.S., a 42 year old white female, had a diagnosis of Hodgkin's disease established by neck node biopsy in April 1939. X-ray therapy was given to the neck with regression of the node. In June 1939 she first came to Memorial Hospital because of rapid onset of paraplegia with respiratory distress. She had complete paralysis of lower extremities and sphincters with sensory level at T 10, right pleural effusion, axillary nodes, and hepatomegaly. Blood pressure was normal. X-rays showed no destruction of vertebrae. Radiotherapy to lumbar and lower thoracic spine was started on the day of admission using 250 KV, 200r daily x 10 (skin dose, in air). After seven days she was able to move her toes. By day 14 she could move her legs slightly. By day 17 there was beginning sensory perception. By 26 days she was standing with support. Further radiotherapy was administered to the lower thoracic spine (1000r) and lumbosacral spine (800r) during the next two months. By October she could walk on the level without assistance. By November she was able to climb stairs and was traveling to clinic alone by bus. She had no further neurologic complications for the thirteen remaining years of her life. Pleural effusion cleared and did not reappear. Active Hodgkin's disease

* The author is indebted to the following staff members of Memorial Cancer Center for permission to report cases from their private or clinic files: Drs. Lloyd F. Craver, Henry D. Diamond, David A. Karnofsky, and Willet F. Whitmore.

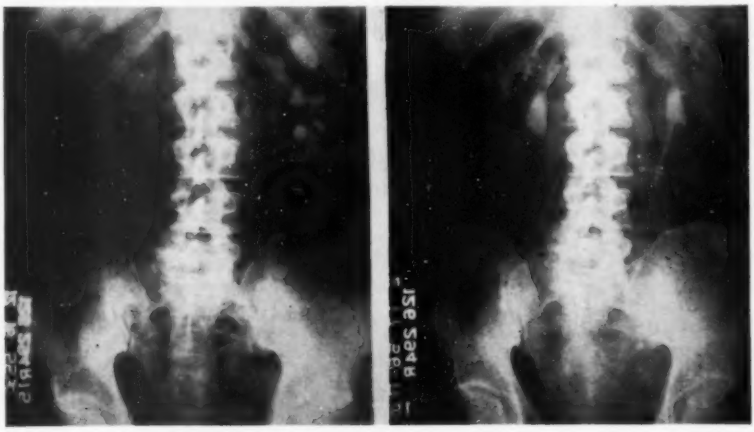

Figure 4—Intravenous pyelograms from case 2 taken before (left) and two months after transplantation of obstructed ureters into sigmoid colon. Note return of function in right kidney and restoration to normal configuration of the left kidney.

was combated by numerous courses of radiotherapy to the abdomen, pelvis, axillae, groins, and breast during the next five years. From 1945 through 1950 there was no evidence of neoplastic disease. In 1946 diabetes was diagnosed and controlled by diet plus variable doses of globin insulin. In 1950 she had left costo-vertebral angle pain, hematuria, oliguria progressing to anuria, blood urea nitrogen of 90mgm/100cc, and hypertension (200/95). Catheterization and retrograde pyelography revealed a calculus obstructing the lower left ureter and a non-functioning congenitally hypoplastic left kidney. Urinary flow was re-established by left nephrostomy and urea nitrogen returned to normal by the fourth postoperative day. Later cystoscopic ureterolithotomy was successful and the nephrostomy tube was removed. For another year the patient was in good health and then started to lose weight progressively. In February 1952 there was hepatosplenomegaly and suggestive evidence of retroperitoneal adenopathy. She was taking 45 units of insulin daily. Blood pressure was 210/110. A week later she was admitted to her local hospital where she died on February 25, 1952. Immediate cause of death has not been ascertained.

Case 2 illustrates successful palliative management of urinary blockage due to tumor mass, and neurological complications.

W.D., a 55 year old white male, had adenocarcinoma of the prostate diagnosed by transurethral resection in April 1954. In June 1954 he was castrated and started on estrogen treatment. He remained clinically well for six months except for progressive frequency, urgency, and gross hematuria. In December 1954 he

was referred to Memorial Hospital where intravenous pyelogram (Figure 4) revealed bilateral hydroureter and hydronephrosis and a nonfunctioning right kidney. The blood urea nitrogen level was normal. Laparotomy revealed carcinoma invading the bladder and pelvic wall and with metastases in pelvic and para-aortic nodes and liver. Bilateral hydronephrosis and hydro-ureter were confirmed. Both ureters were transplanted to the sigmoid colon (Leadbetter technique). Postoperative recovery was uneventful and the patient was asymptomatic except for frequent voiding per rectum. Pyelograms revealed normal function and configuration of both kidneys (Figure 4). The blood urea nitrogen remained normal for the remainder of the patient's life. In January 1956 he developed intrapelvic pain, and weakness of the left thigh and paraspinal muscles. The primary tumor mass had increased in size, was invading the rectal mucosa, and had diminished the caliber of the rectal lumen. Million-volt x-ray therapy was directed to pelvic and para-aortic portals with prompt relief of these problems. Since there was no evidence of hepatomegaly or impaired liver function from the known metastatic disease, the radiotherapy was continued to full therapeutic doses of approximately 4,000r tumor dose. For the next three months the patient had no complaints, gained weight, and was working full time. In May 1956 he had nausea and anorexia and rapid weight loss of 10 pounds. He had no other symptoms and there was no evidence by physical examination, x-rays or laboratory tests of progression of disease in pelvis, liver, lungs, or bones. The following week he felt better but had fever for which antibiotics were empirically prescribed. He was not seen again at this hospital and expired at home on July 2, 1956. Immediate cause of death is not known.

Case No. 3 illustrates the usefulness of nitrogen mustard treatment preceeding radiotherapy to a superior mediastinal mass. This case is presented instead of one with a more spectacular therapeutic result because this was the first case of lung cancer to be treated by chemotherapy at Memorial Hospital.

M.B., a 60 year old white male, had progressive weakness and weight loss starting about April 1945 and onset of pain in the right upper chest and shoulder in August. He first sought medical attention in October 1945 at which time x-rays showed atelectasis and a mass obliterating the right upper lung field (Figure 5). An axillary node biopsy showed only hyperplasia but diagnosis of anaplastic carcinoma was established by aspiration biopsy from the intrathoracic mass. During the period of these diagnostic studies serial x-rays showed progression of the right upper lung lesion followed by massive pleural effusion. It was felt that radiotherapy to such a rapidly growing lesion was contraindicated because of the danger of edema leading to asphyxia. Treatment with nitrogen mustard (HN2) was started November 20, 1945, using doses of 0.1 milligrams per kilo I.V. for a total of 0.6 milligrams per kilo in eight days. Both subjective and objective improvement was apparent starting four days after chemotherapy. After 10

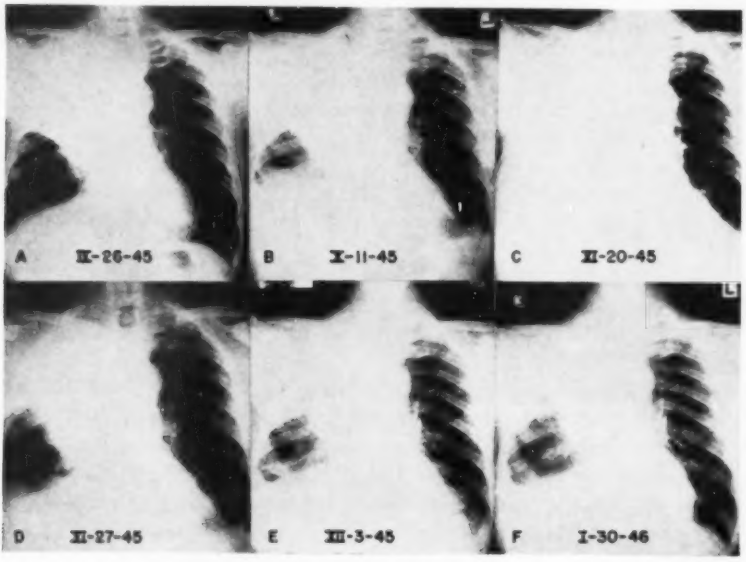

Figure 5—Serial chest x-rays on case 3. Dates are indicated on the figure. Top three films show progressive disease pre-treatment. D is 7 days after first dose of HN2. E is 13 days after first HN2 and pre-x-ray. F is 8 weeks after start of x-ray therapy to right upper lobe.

days dyspnea had disappeared, vital capacity had increased from less than 1,000 to 1,800 cc., nodes had shrunk, pleural effusion and venous congestion had diminished, and there had been a 15 pound diuresis. Million-volt radiotherapy was started December 3 giving 150r every two days to alternate anterior and posterior portals up to a total of approximately 3,500r tumor dose in seven weeks. During December, January, and February the patient's status was comparatively good. Vital capacity increased to 2,300 cc., pleural effusion and venous congestion completely cleared, and there was no further weight loss. The patient returned to restricted work as a janitor. Late in February he had recurrence of dyspnea, venous congestion, and weight loss. Thereafter he rapidly deteriorated. He failed to respond to a second course of treatment with HN2 and died April 11, 1946.

This patient was palliated for about three months and probably survived an additional three months as a result of the treatment. At present we would treat more rapidly. The entire course of nitrogen mustard would probably be given in one injection. The x-ray treatment would be started immediately after chemotherapy and would be given more rapidly. The period of hospitalization would be greatly reduced.

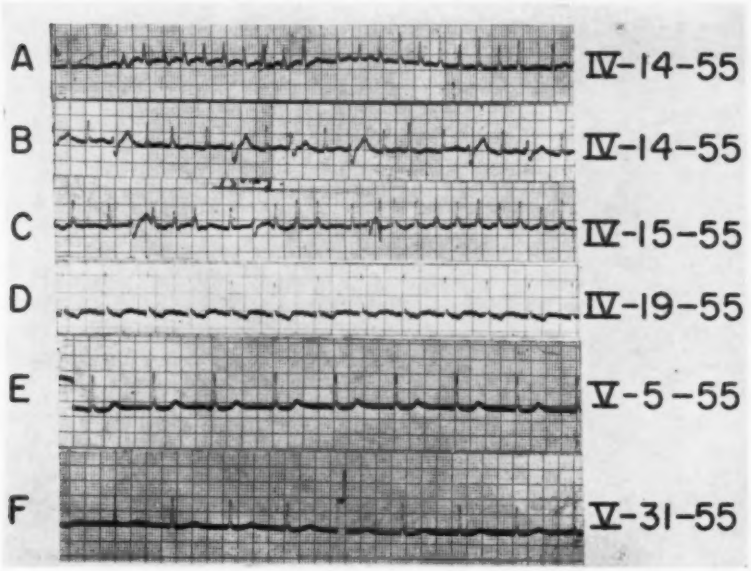

Figure 6—Serial electrocardiograms of case 4. All records are lead II. A. shortly after admission, paroxysmal tachycardia with electrical alternans, no change from carotid pressure. B. after Cedilanid 0.8 mg. I.V. trigeminal rhythm with ventricular premature contractions. C. during administration of Pronestyl 150 mg. I.V., transient suppression of VPCs but sustained tachycardia. D. After full digitalization, persistent auricular tachycardia with 2:1 block, digitalis effect. (Note time scale slightly greater than in other records). Radiotherapy to heart started this date. E. 14 days after start of radiotherapy. Reversion to normal sinus rhythm, digitalis effect. Approximately 500r tissue dose to heart by this time. F. essentially normal tracing. Total tissue dose of x-ray to heart approximately 1500r. No digitalis.

Case 4 illustrates an unusual complication of cancer due to organ infiltration. She presented a difficult diagnostic problem which was successfully palliated by local irradiation.

R.S., a 54 year old colored woman had reticulum cell sarcoma which was diagnosed by neck node biopsy in March 1955, three months after cervical adenopathy was first noted. She came to Memorial Hospital in April 1955 with night sweats, pallor (hgb 11gm.), generalized adenopathy, intra-abdominal masses, mediastinal widening, and tachycardia with poor heart sounds. Cardiac rate was 160, blood pressure 90/60, a thyroid nodule was palpable but thyroid function studies including a radioactive iodine tracer study were normal. Electrocardiogram (Figure 6) showed ventricular paroxysmal tachycardia with electrical alternans. Successive treatment by carotid pressure, intravenous Pronestyl, and digitali-

TABLE I.—NEW CASES OF INCURABLE CANCER IN THE UNITED STATES PER YEAR IN THOUSANDS

Origin of Cancer	*Total New Cancer Cases*	*Actual Results*		*Optium Results*	
		Per cent 5 Year "Cures"	*Number of Cases NOT Curable*	*Per cent 5 Year "Cures"*	*Number of Cases NOT Curable*
Skin & Lip	46.9	67	15.5	74	12.5
Mouth	11.5	32	8.7	68	3.7
Lung	25.0	4	24.0	50	12.6
G.I. Tract	134.0	17	110.0	43	77.0
Breast	49.0	46	26.3	70	15.0
Uterus	36.5	55	16.5	87	4.8
Ovary	10.5	24	8.0	55	4.7
Prostate	21.7	21	17.3	34	14.4
Testis	2.0	25	1.5	40	1.2
KUB Tract	21.0	28	15.1	47	11.1
RE System	23.8	1	23.6	1	23.6
Thyroid	2.5	40	1.5	?	?
Other	31.9	5	22.6	9	20.7
ALL	416.3	35	291.6	52	202.8

zation to toxicity produced no improvement in the electrocardiogram or clinical status. On April 21 radiotherapy to the anterior and posterior heart was started. For the next few days there was no change, but on May 4 pulse reverted to normal rhythm and EKG was normal except for evidence of digitalis effect. X-ray dosage to this time totaled 425r (in air, skin dose) anterior and posterior. It was continued to 1625r each port. Digitalization was discontinued. During August 1955 the patient had productive cough, wheezing, pulmonary infiltrates by chest roentgenogram, abdominal fullness, and ankle edema. She received intravenous HN2 followed by maintenance doses of TEM for a few weeks. All these signs and symptoms disappeared and the hemoglobin rose spontaneously to normal levels. The patient has returned to full activity which included singing in her church choir. There was no recurrence of cardiac dysfunction, or other evidence of disease activity, at the time of her most recent clinic visit (July 1956).

To conclude this discussion of the management of incurable cancer it may be worth while to consider the magnitude of the problem and the frequency with which we can offer palliation. Table I summarizes the estimated incidence and curability of cancer in the United States.

TABLE II.—THE VALUE AND DEFICIENCIES OF CANCER CHEMOTHERAPY. ESTIMATED NUMBERS OF NEW INCURABLE CANCER PATIENTS IN THE UNITED STATES PER YEAR WHO CAN OR WHO CAN NOT BE PALLIATED BY PRESENT ANTI-NEOPLASTIC DRUGS

Origin of Cancer	*New Incurable Cancer Cases*	*Response Rate to Present Chemotherapy*		*Number of Incurable Cases Per Year Receiving:*	
		percent	*reference*	*Some benefit from present chemotherapy*	*No benefit from present chemotherapy*
RE System	23.6	90	*	21.2	2.4
Prostate	17.3	70	4	12.1	5.2
Thyroid	1.5	80	6	1.2	0.3
Testis	1.5	60	*	1.0	0.5
Lung	24.0	50	7	12.0	12.0
Breast	26.3	40	5	10.5	15.8
Ovary	8.0	30	7	2.4	5.6
Skin, Mouth, GI Uterus, KUB, Other	189.4	0	*	0	189.4
ALL	291.6	21		60.4	231.2

* When no reference is listed the tabulated response rate is the author's estimate based on experience of the Chemotherapy Service of Memorial Cancer Center. Cancer incidence and curability figures are based on statistics from Connecticut for 1947-51.[8]

These figures are based on the 1947 to 1951 statistics from the Connecticut State Cancer Registry[8] and have been extrapolated to a total U.S. population of 150,000,000. The figures for present curability are based on five year survivals after subtracting deaths due to causes other than cancer. They are probably falsely high because (except for leukemias) five year survivals are considered as cures. Optimum curability rates were estimated on the basis of five year "cures" in those patients who had only localized disease at the time of first treatment. These figures give an indication of what could be accomplished by present curative procedures if cancer detection were accomplished with maximum efficiency and treatment initiated promptly. These data indicate that the over-all cure rate for cancer is about 35 per cent and the greatest cure rate which might be expected with present methods of treatment is about 50 per cent. It follows that there are approximately 300,000 new incurable cancer patients each year and (assuming an over-all mean survival time of about two years) over a half-million persons

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living with incurable cancer at the present time. If these patients were distributed equally among the approximately 200,000 registered physicians in the United States it would mean an average permanent case load of three incurable cancer patients per doctor.

Table II presents estimated response rates to currently available methods of chemotherapy. The sources of these data are indicated in the table. In the lymphomas and leukemias, and breast and prostate cancers, the numbers of patients who receive significant palliation is gratifying, but the duration of palliation is a few years at best and often lasts only a few months. Eighty per cent of all incurable cancer patients can expect no worth while effect from any type of systemic chemotherapy.

These figures carry many implications. They emphasize the tremendous need for research in the fields of prevention, detection, improved surgery and radiotherapy, and new methods of chemotherapy. They are not completely discouraging, for we are entitled to recall that almost all the palliative procedures which we now use are the products of research of the past two decades. These figures emphasize by their very magnitude our obligation as physicians to be aware of and to apply whatever palliative measures we do now have. And finally, they state indisputably that the management of incurable cancer is not a problem for the specialist alone, but is of necessity a problem that is encountered by and must be managed by every medical practitioner.

REFERENCES

1. Kuschner, M. and Thomas, L. Management of disseminated neoplastic disease. I. Complications due to infections, *Bull. N.Y. Acad. Med. 33*:684-92, 1957.
2. Ley, A. and Ellison, R. R. Management of disseminated neoplastic disease. II. Hematologic problems, *Bull. N.Y. Acad. Med. 33*:693-703, 1957.
3. Myers, W. P. L. Management of disseminated neoplastic disease. III. Metabolic disturbances, *Bull. N.Y. Acad. Med. 33*:704-19, 1957.
4. Whitmore, W. F. Hormone therapy in prostatic cancer, *Amer. J. Med. 21*:697-713, 1956.
5. Pearson, O. H., and others. Management of metastatic breast cancer, *J. Amer. med. Assoc. 159*:1701-04, 1955.
6. Sonnenberg, M. and Rall, J. E. The use of radioactive iodine in cancer of the thyroid, *Med. Clin. N. Amer. 40*:821-36, May 1956.
7. Sykes, M. P., Phillips, F. S. and Karnofsky, D. A. Comparative therapeutic activity of the nitrogen mustards and allied compounds, *Med. Clin. N. Amer. 40*:837-56, May 1956.
8. Griswold, M. H., Wilder, C. S., Cutler, S. J., and Pollack, E. S. *Cancer in Connecticut 1935-1951*. Hartford, Connecticut State Department of Health, 1955.

JOHN STEARNS, 1770-1848
THE ACADEMY'S FIRST PRESIDENT

JOHN STEARNS personifies the link between colonial and modern medicine. Born before the Revolution, of a physician father, he received a rather better than normal medical education for the period: Yale College, followed by apprenticeship to a country doctor, then lectures at the Philadelphia medical school under Shippen, Wistar, Rush and others. Settling in Saratoga County in 1793, he engaged in extensive and laborious rural practice, still in pioneering conditions for he had to tie his horse to a tree and cross the Mohawk on a log to reach his Dutch settler patients.

These severe early years laid the groundwork for his life's work Here he observed both the detail and the mass: he learned and promulgated the parturient properties of ergot, treated tuberculosis successfully, studied the prevalence of disease in Saratoga County and croup and influenza in Waterford, laying a firm foundation of experience on which to form later mature conclusions and to write thoughtful papers.

These years, too, showed him the usurpation of medical practice by charlatans and the gross controversies of consultants at a patient's bedside. To counteract these deplorable conditions, Stearns joined with two other physicians in attempting to establish a society for combating empiricism and quackery and encouraging regular practitioners. Once approved by the Legislature, these efforts resulted in the formation of 20 county societies in 1806 in less than three months and in that of the State Society in 1807, with Stearns as the latter's secretary for the first seven years, and president 1819-21. This show of public spirit was probably instrumental in sending him to the State Legislature for four years, 1810-13. As early as 1812, his services to general education and his distinguished attainments in medicine earned him an honorary M.D. from the New York State Board of Regents.

It may be considered fortunate for the Academy that following his Albany years he took up practice in New York City at the instigation of his former patients, DeWitt Clinton and Daniel D. Tompkins. Here

the same power of thoughtful observation (he studied and mapped the yellow fever epidemic of 1819-22), much of it among the poor, combined with a realization of the continuing unsatisfactory conditions of medical ethics, made him a moving spirit among the group of physicians who united to combat the situation and in 1847 formed The New York Academy of Medicine. This does not mean that the Academy would not have been formed without Stearns, but he typifies the hard-working regular physician of the time, exerting his influence to promote public health education and to counteract ignorance and empiricism. Fittingly enough, this faithful worker for the welfare of his fellows and the honor of his profession, then in his 76th year and dean of the medical community, was elected the Academy's first president. His qualities as a presiding officer were admirable: a thorough knowledge of procedure, ready tact, sound judgment, and ability for impartial action.

Deeply religious, Stearns was not only a dedicated physician but a devoted husband and father. His letters to his daughter exhibit much affectionate moralizing as well as educational ideas in advance of his time. "Let nothing interfere with the hours which you devote to reading.... Too many of your sex are always silent whenever any subject is started except what relates to fashion, character, or amusements." Stearns' care for his patients was assiduous throughout his long practice, and led, alas, directly to his death. One morning after paring an apple, he grazed the skin of his thumb when shutting his penknife. Attending a patient with erysipelas soon afterwards, he developed symptoms of the disease himself the next day and quickly succumbed.

Stearns' importance lies not so much in what he *did*, but in what he *was*. His achievements in his profession were neither bold nor brilliant. But through a long life he devoted himself to the care of the sick, to profiting from what he learned, and to advancing the interests and contributing to the science of his profession. He was one of those who, rooted in a previous era, grew with the times, nourished new ideas, and saw the happy advancement of the ideals for which he had spent his life.

Janet Doe, *Library Consultant*
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SEE FOLLOWING PAGES FOR PROGRAM

POSTGRADUATE WEEK PROGRAM–OCTOBER 7 to 11

EVENING LECTURES – 8:30 P.M.

OCTOBER

7th

THE STRUCTURE AND DEVELOPMENT OF VIRUSES REVEALED BY THE ELECTRON MICROSCOPE
Councilman Morgan, *College of Physicians and Surgeons, Columbia University*

IMPLICATIONS OF 60 NEWLY RECOGNIZED VIRUSES OF MAN
Robert J. Huebner, *National Institutes of Health, Bethesda, Md.*

CLINICAL ASPECTS OF VIRAL DISEASES
Robert Ward, *New York University College of Medicine*

8th

ASPECTS OF CARBOHYDRATE AND PHOSPHATE METABOLISM IN DIABETES
William C. Stadie, *University of Pennsylvania School of Medicine*

FAT METABOLISM IN DIABETES
Vincent P. Dole, *The Rockefeller Institute for Medical Research*

MODERN ASPECTS OF THE DIABETES PROBLEM
Garfield G. Duncan, *University of Pennsylvania School of Medicine*

9th

DISTURBANCES OF AMINO ACID METABOLISM
L. Emmett Holt, Jr., *New York University College of Medicine*

CONNECTIVE TISSUES IN MEDICINE AND SURGERY
Jerome Gross, *Harvard Medical School*

CURRENT CONCEPTS OF THE HOMOPLASTY ENIGMA
Richard B. Stark, *College of Physicians and Surgeons, Columbia University*

(Continued on next page)

POSTGRADUATE WEEK PROGRAM – *continued*

EVENING LECTURES – 8:30 P.M. – *continued*

OCTOBER

10th

POTASSIUM AND THE KIDNEY
Gilbert H. Mudge, *The Johns Hopkins University School of Medicine*

RENAL TUBULAR DYSFUNCTION IN CONGESTIVE HEART FAILURE
Louis Leiter, *College of Physicians and Surgeons, Columbia University*

RENAL EXCRETION OF URIC ACID IN GOUT: MODIFICATION BY URICOSURIC AGENTS IN TREATMENT
Alexander B. Gutman, *College of Physicians and Surgeons, Columbia University*

11th

CURRENT VIEWS ON THE BIOCHEMISTRY AND PHYSIOLOGY OF MYOCARDIAL CONTRACTION
H. Mead Cavert, *University of Minnesota Medical School*

PHYSIOLOGY OF HYPOTHERMIA
James E. Eckenhoff, *University of Pennsylvania Schools of Medicine*

THE PRESENT STATUS AND THE PROBABLE DIRECTION OF FUTURE DEVELOPMENTS IN OPEN CARDIOTOMY IN THE CORRECTION OF CARDIAC DEFECTS
John H. Gibbon, Jr., *The Jefferson Medical College*

PANEL MEETINGS – 3:30 P.M.

7th

THYROID DISEASE
Chairman: Rulon W. Rawson, *Memorial Center for Cancer and Allied Diseases*

8th

ADRENAL GLAND AND ADRENAL TUMORS
Chairman: Joseph W. Jailer, *College of Physicians and Surgeons, Columbia University*

9th

MODERN ASPECTS OF HEMATOLOGY
Chairman: Irving M. London, *Albert Einstein College of Medicine, Yeshiva University*

10th

PRACTICAL APPLICATION OF RADIOACTIVE METALS
Chairman: Lee E. Farr, *Brookhaven National Laboratory Hospital*

11th

BLOOD PROTEINS
Chairman: Henry G. Kunkel, *The Rockefeller Institute for Medical Research*

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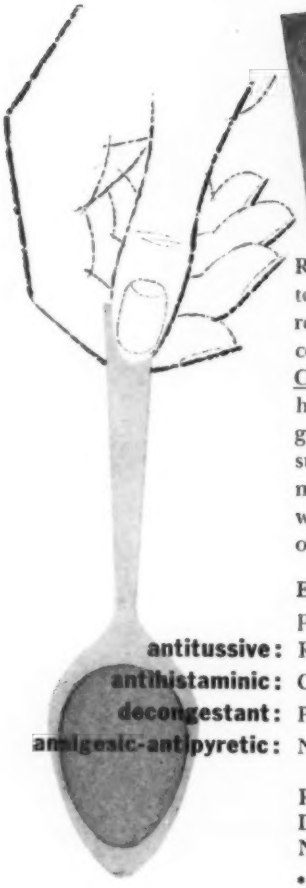

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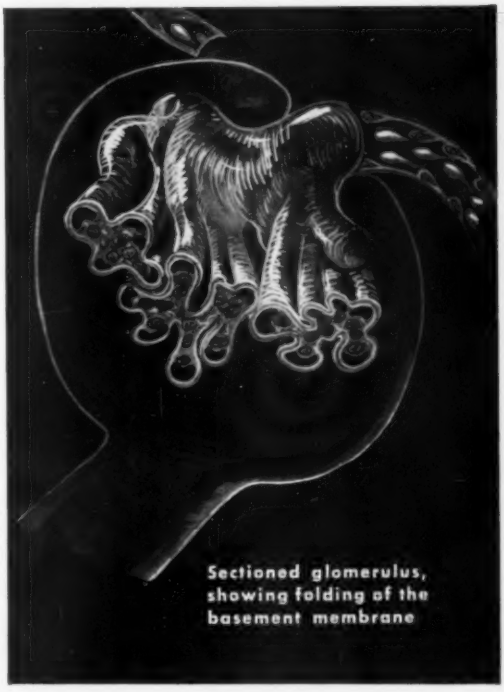

Sectioned glomerulus, showing folding of the basement membrane

*Settel, E.: Rolicton® (Aminoisometradine), a New, Nonmercurial Diuretic, Postgrad. Med. *21*:186 (Feb.) 1957.

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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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references: 1. Carne, S.: Brit. M. J. 2:827 (Oct. 6) 1956.
2. Giordano, A. S.; Pope, J. L., and Hagan, B.: Am. J. M. Technol. 22:29. 1956.

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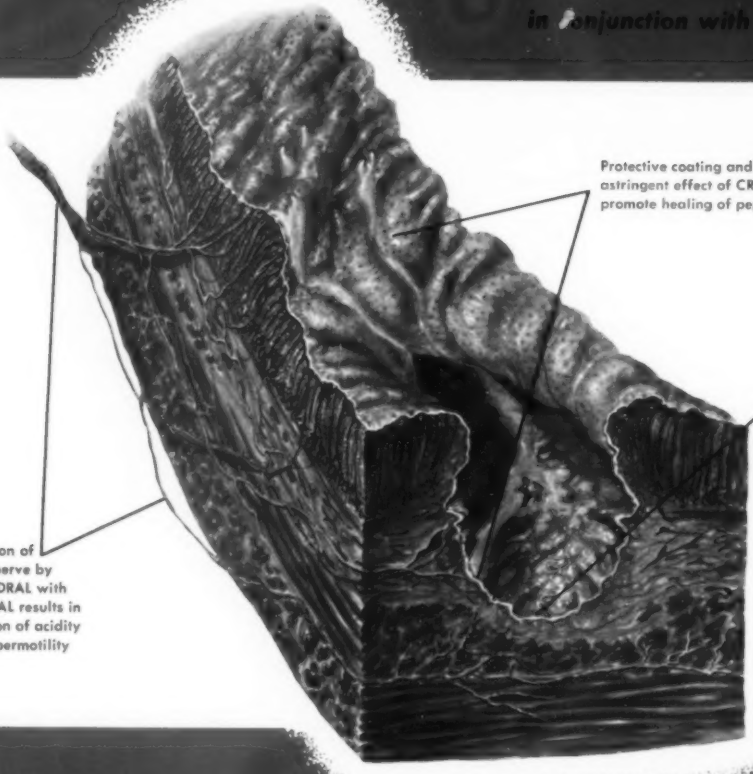
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Creamalin tablets — bottles of 50 and 200.

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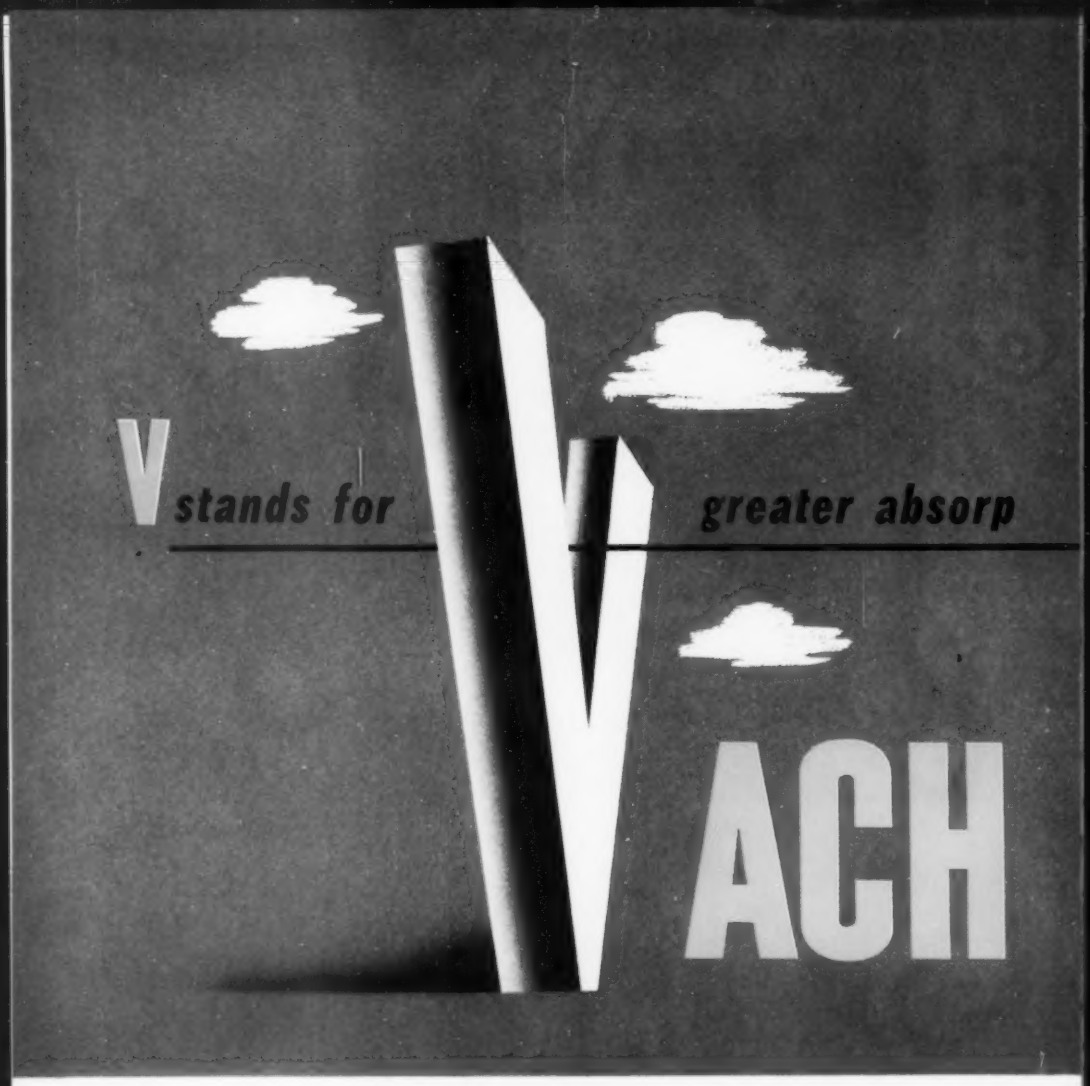

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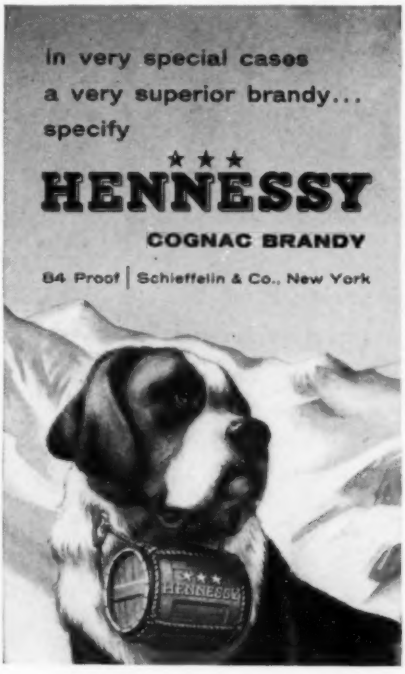

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OLEANDOMYCIN TETRACYCLINE-PHOSPHATE BUFFERED

. . .

buffered for higher, faster antibiotic levels . . . adds new certainty in antibiotic therapy . . . *particularly for that 90% of the patient population treated at home or office when susceptibility testing is* not *practical*—

Supplied:

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SIGNEMYCIN† CAPSULES—250 mg. (oleandomycin 83 mg., tetracycline 167 mg.), bottles of 16 and 100; 100 mg. (oleandomycin 33 mg., tetracycline 67 mg.), bottles of 25 and 100.

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• lowers blood pressure gradually • induces a sense of well-being
• negligible, if any, side effects

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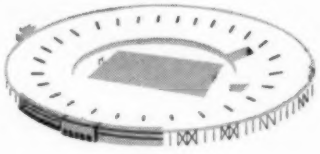

Each Veratrite tabule contains:

Cryptenamine (tannates)	40 C.S.R.† Units
Sodium nitrite	1 gr.
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†Carotid Sinus Reflex

*The number of patients treated successfully with these prescriptions would fill the Rose Bowl 88 times.

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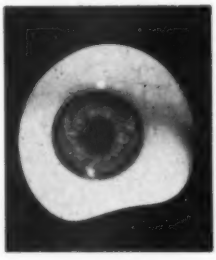

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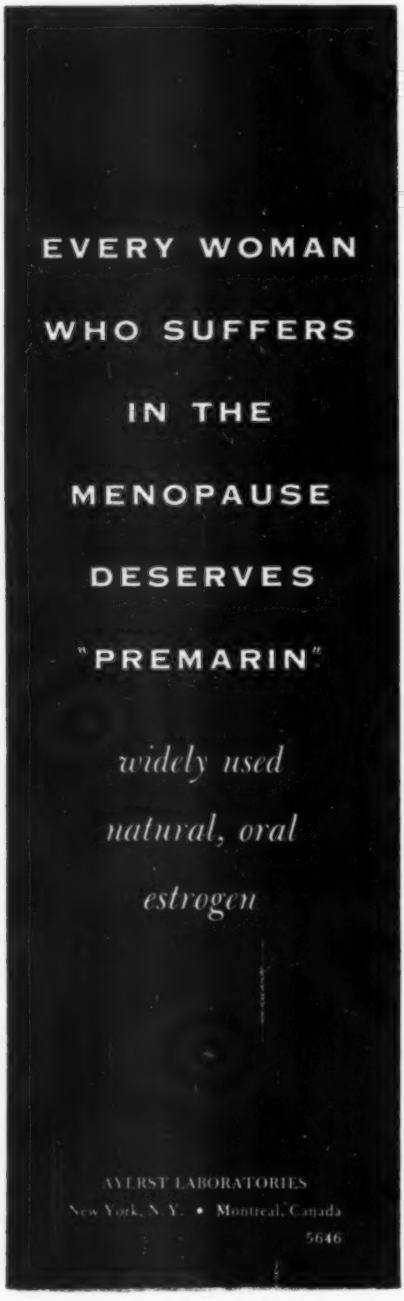

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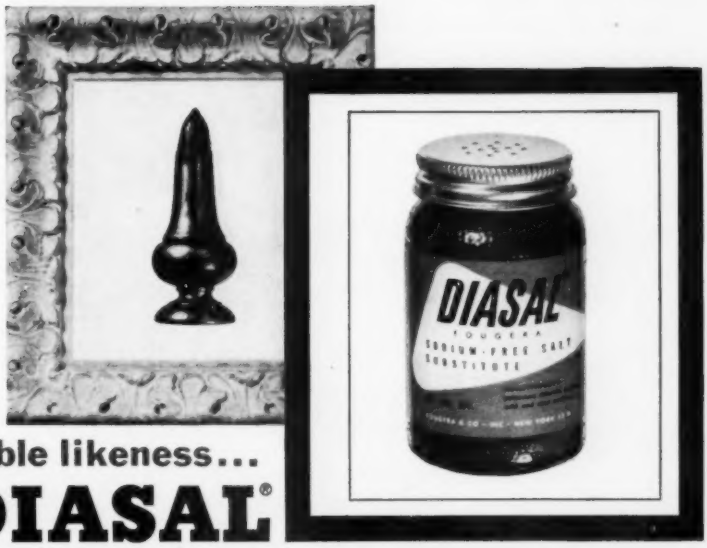

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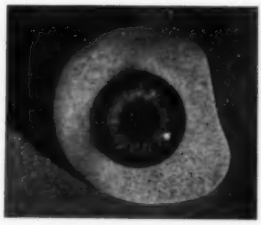

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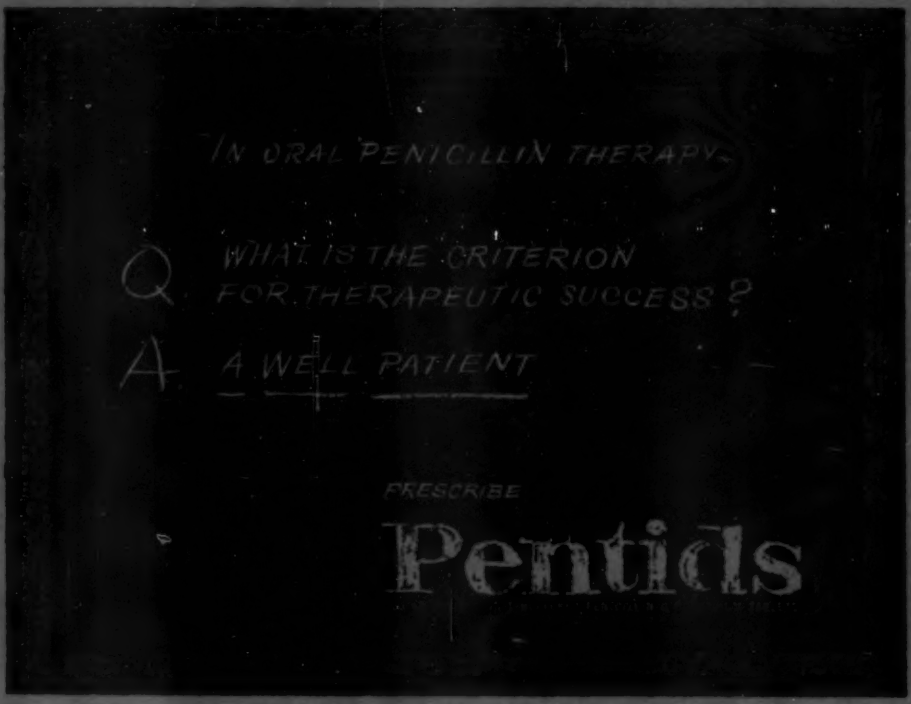

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